Infectious Diseases of the Nervous System

Burk Jubelt

In this chapter infectious diseases of the nervous system are discussed. These include bacterial, viral, fungal, spirochetal, and parasitic infections. Although the central nervous system (CNS) is protected from bacterial invasion by the intact blood-brain barrier, bacterial invasion is enhanced by the special surface properties of bacteria as well as host immune deficiencies. Similar to any type of infection of the nervous system, bacteria may involve any of the nervous system compartments: the epidural space (epidural abscess); the dura (pachymeningitis); the subdural space (subdural empyema); the leptomeninges and the subarachnoid space containing cerebrospinal fluid (meningitis or leptomeningitis); and the brain parenchyma (brain abscess). The clinical manifestations, pathogenesis, pathology, etiology, epidemiology, diagnosis, differential diagnosis, and treatment of these syndromes are presented.

The list of viruses capable of causing neurologic disease is extensive. Most viral infections of the nervous system represent unusual complications of common systemic infections. After replication in extraneural tissue, viruses reach the CNS by the bloodstream or spread along nerve fibers. Although rabies and poliomyelitis have been known since antiquity, only in the early part of the twentieth century were they demonstrated to be caused by "filterable agents" (viruses). In the 1930s, arboviruses were isolated from the brains of patients dying of encephalitides (Eastern and Western equine, St. Louis, and Japanese encephalitis), and lymphocytic choriomeningitis virus was isolated from the spinal fluid of patients with aseptic meningitis, being the first virus demonstrated to cause this syndrome. The coxsackie- and echoviruses were isolated and recognized to cause viral meningitis in the 1950s. The 1960s and 1970s were the decades during which slow virus infections were recognized, with conventional viruses and atypical agents (prions) isolated from chronic neurologic diseases. The 1980s ushered in the identification of the retroviruses with the AIDS epidemic and tropical spastic paraparesis. In the late 1990s, West Nile virus began to cause disease in North America. We have yet to discover what other viruses are unrecognized as causes of unusual neurologic diseases.

The past 30 years have seen a steady increase in the frequency of fungal infections of the CNS, primarily due to the increased use of immunosuppressive drugs and the AIDS epidemic. Most fungal infections are caused by opportunistic organisms except those caused by the pathogenic fungi (histoplasmosis, blastomycosis, coccidioidomycosis, and paracoccidioidomycosis). In most fungal infections, spread to the CNS occurs after obvious extraneural primary infection of the lungs, skin, and hair, the main exception being cryptococcosis.

The spirochetal diseases that involve the nervous system include syphilis, Lyme disease, and leptospirosis. Syphilis and Lyme disease regularly cause both meningeal and parenchymal disease; humans are the only host in syphilis and an important dead-end host in Lyme disease. Both of these diseases can be chronic and are relatively common; they are discussed in detail. Leptospirosis, in contrast, is a disease of both wild and domestic animals with humans being incidental hosts. Human infection occurs through contact with infected animal tissue or urine or from exposure to contaminated ground water, soil, or vegetation. Leptospirosis is a self-limited illness that primarily manifests as aseptic meningitis. Rarely, encephalitis, myelitis, optic neuritis, and peripheral neuropathy have been reported. Penicillin (or tetracycline as an alternative therapy) is the antibiotic of choice; fewer than 100 cases of leptospirosis are reported per year.

CHAPTER 12

R. N. Rosenberg (ed.), *Atlas of Clinical Neurology*

Parasitic infections can be divided into two major categories: protozoan and helminthic (worms). Helminths include nematodes (roundworms), trematodes (flukes), and cestodes (tapeworms). Parasitic diseases occur worldwide but are most common in tropical and underdeveloped areas of the world, where poverty and poor housing conditions contribute to their pathogenesis and spread. Tropical climates are also ideal for the vectors that spread these infections. In these areas, parasitic infections are the most common infectious disease, and they exact a heavy toll on the human population.

Bacterial Infections

Acute Bacterial Meningitis

Clinical Manifestations of Acute Bacterial Meningitis By Age Group

Age Group	Symptoms	Signs
Infants (≤ 2 years)	Irritability	Fever
	Poor feeding	Lethargy
	Vomiting	Stupor, coma
	Unconsciousness	Bulging fontanel
	Respiratory symptoms	Seizures
	Apnea	Petechial or purpuric rash
Children and adults	Headache	Fever
	Neck stiffness or pain	Nuchal rigidity
	Unconsciousness	Lethargy, confusion, stupor, coma
	Nausea and vomiting	Seizures
	Photophobia	Focal neurologic deficits, including cranial nerve palsies
	Respiratory symptoms	Ataxia (in children)
		Petechial or purpuric rash

Figure 12-1. Clinical manifestations of acute bacterial meningitis by age group. The symptoms and signs of bacterial meningitis in infants are nonspecific and typical of a severe systemic infection including sepsis. In children and adults, the classic signs of meningeal irritation are nuchal rigidity, Kernig's sign, and Brudzinski's sign. Nuchal rigidity is present when the patient has resistance to passive flexion of the neck. Kernig's sign is elicited by flexing the thigh and knee while the patient is in the supine position; in the presence of meningeal inflammation, there is resistance to passive extension of the leg at the knee with the thigh flexed. Brudzinski's sign is positive when passive flexion of the neck causes flexion of the hips and knees. Neurologic complications are frequently associated with bacterial meningitis. Seizures occur in 40% of cases. Generalized seizures usually occur early due to fever, metabolic derangements, or toxic factors (*eg*, alcohol withdrawal); focal seizures are more likely to occur after 4 to 10 days and are caused by arterial thrombosis, cortical vein thrombosis, or abscess formation. Cranial nerve (CN) palsies, especially of CN III, VI, VII, and VIII, are due to purulent exudates in the arachnoid sheaths of the specific cranial nerve. Sensorineural hearing loss is a major complication in infants and children, occurring in 30% of cases. Cerebral edema and increased intracranial pressure may be due to noncommunicating hydrocephalus caused by basilar exudates, or to exudates in the Virchow-Robin spaces invading the parenchyma. Focal cerebral signs are most likely to occur at the end of the first week of infection but may occur later as well; they are due to arterial thrombosis causing infarction, cortical vein thrombosis with secondary hemorrhagic infarction, or abscess formation.

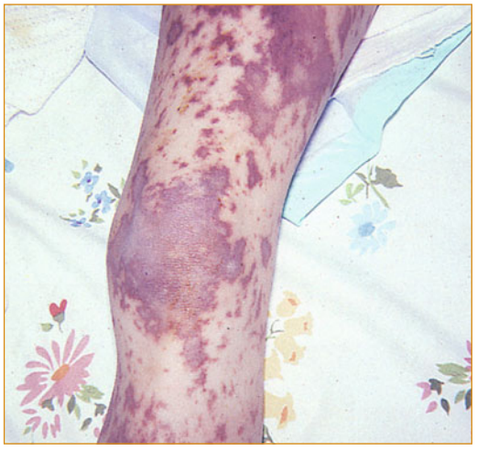


Figure 12-2. Meningococcal rash. Meningococcus is the only bacterium that frequently causes a rash, which is probably the most important clue to the diagnosis of meningococcal meningitis. It usually begins as a diffuse erythematous maculopapular rash. As the rash evolves, petechiae and purpura appear primarily on the trunk and lower extremities. (*From* Roos *et al*. [1]; with permission.)

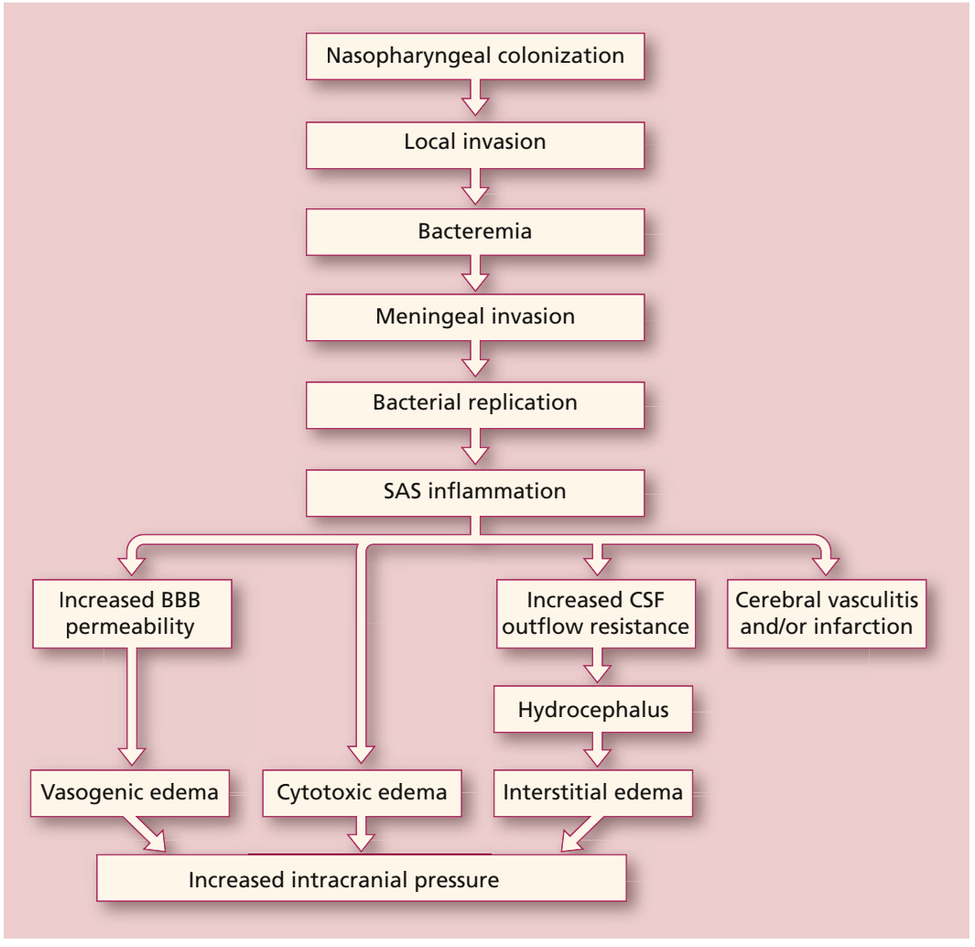


Figure 12-3. Pathogenesis of meningitis. For bacterial meningitis to occur, the host usually acquires a new organism by colonization of the nasopharynx. This may lead to direct seeding of cerebral spinal fluid (CSF) spaces, but more likely causes local spread to the sinuses or the lungs (pneumonia) or bacteremia, which then results in meningeal invasion. BBB—blood-brain barrier; SAS—subarachnoid space. (*Adapted from* Roos *et al*. [1].)

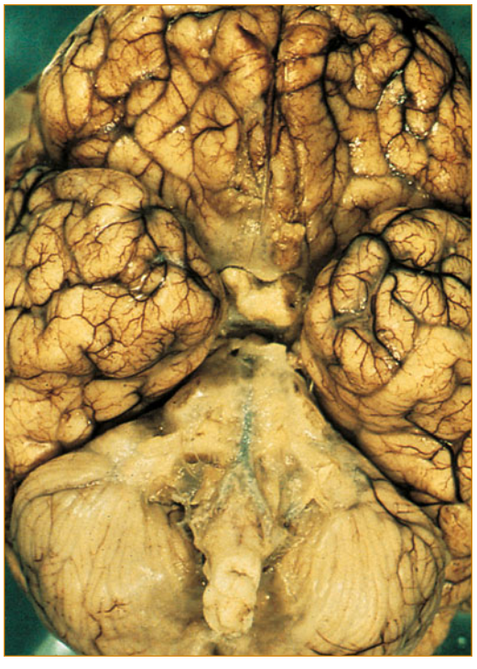


Figure 12-4. Purulent exudate of bacterial meningitis at the base of the brain. The neurologic complications of cranial nerve palsies and increased intracranial pressure are often caused by inflammation of the base of the brain. The increased intracranial pressure occurs because cerebrospinal fluid pathways are blocked, resulting in obstructive hydrocephalus. (*From* Roos and Bonnin [2].)

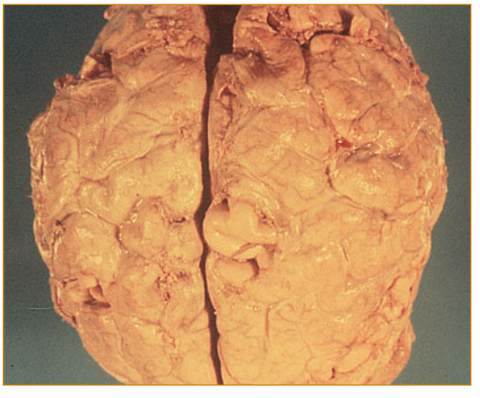
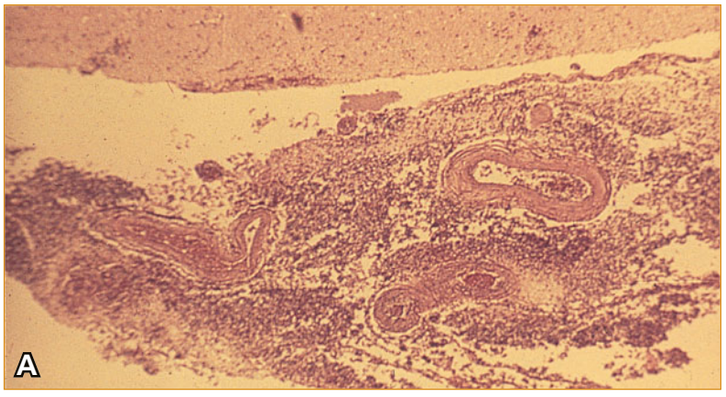


Figure 12-5. Purulent exudate of leptomeningitis (inflammation of pia and arachnoid spaces) over the convexities of the cerebral cortex. This may result in the additional complications of arterial or venous thrombosis with infarction and hemorrhage, both of which may lead to focal neurologic defects. Initially exudates over the convexity appear yellow, but later turn gray as they become thicker. (*From* Kaplan [3]; with permission.)



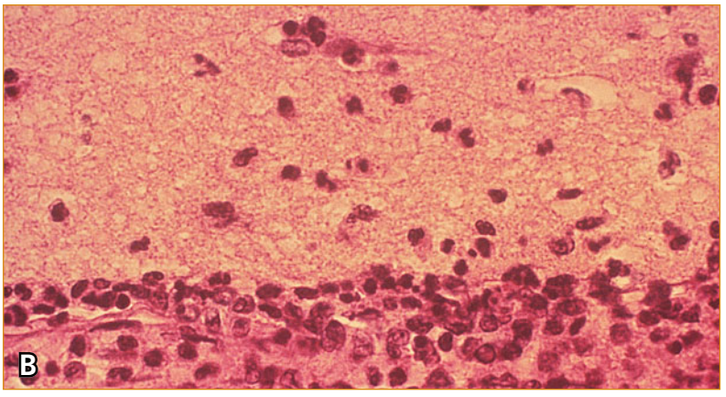


Figure 12-6. Microscopic examination in bacterial meningitis. **A**, The meninges are thickened by both polymorphonuclear and mononuclear inflammatory cells. Thickening of blood vessels may eventually lead to thrombotic occlusion, cerebral infarcts, and focal neurologic deficits. **B**, Inflammatory cells in the Virchow-Robin spaces around penetrating parenchymal vessels. The Virchow-Robin spaces are an extension of the subarachnoid space. Occasionally, inflammation may extend into the perivascular parenchyma, as shown here. (**A**, *from* Kaplan [3]; with permission; **B**, *from* Wilson [4]; with permission.)

Predisposing Factors in 404 Single Episodes of Bacterial Meningitis

Factor	Community-acquired, % (*n* = 253)	Nosocomial, % (*n* = 151)
Acute otitis media	19	1
Chronic otitis media	7	0
Sinusitis	12	4
Pneumonia	15	8
Endocarditis	7	1
Head injury*		
Recent	5	13
Remote	4	0
Recent neurosurgery*	0	68
Neurosurgical device†	1	32
Altered immune state	19	31
Diabetes mellitus	10	6
Alcoholism	18	5
Cerebrospinal fluid leak	8	13
None of the 13 factors	25	8

**Recent denotes head injury or neurosurgery within 1 month of the onset of meningitis; remote, more than 1 month before the onset of meningitis.*
†Neurosurgical devices included ventriculostomy, ventriculoperitoneal or ventriculoatrial shunt, lumbar epidural catheter, lumboperitoneal catheter, and dorsal-column stimulator.

Figure 12-7. Predisposing factors in bacterial meningitis. Predisposing factors for community-acquired meningitis are somewhat different than those seen in nosocomial infections. Predisposing factors for nosocomial infections are primarily caused by openings into the central nervous system. (*Adapted from* Durand *et al*. [5].)

Percentage of Causative Organisms in Single Episodes of Meningitis, 1962 Through 1988*

Organism	Community-acquired, % (*n* = 253)	Nosocomial, % (*n* = 151)
Streptococcus pneumoniae	38	5
Gram-negative bacilli†	4	38
Neisseria meningitidis	14	1
Streptococci‡	7	9
Enterococcus	0	3
Staphylococcus aureus	5	9
Listeria monocytogenes	11	3
Haemophilus influenzae	4	4
Mixed bacterial species	2	7
Coagulase-negative staphylococci	0	9
Other§	2	3
Culture negative	13	11

**Percentages do not always total 100 because of rounding.*
†In community-acquired meningitis, the causative organisms were Escherichia coli (4 episodes), and species of Klebsiella (3), Enterobacter (1), and Proteus (1); in nosocomial meningitis, E. coli (17), Klebsiella (13), Pseudomonas (6), Acinetobacter (6), Enterobacter (5), Serratia (5), Citrobacter (2), Proteus (1), "coliform" bacteria (1), and "nonenteric gram-negative rods" (1).
‡In community-acquired meningitis, the causative organisms were group A (4 episodes), group B (1), nonenterococcal group D (3), group D, not further identified (1), other groups (5), and nonhemolytic, nongrouped (3); in nosocomial meningitis, the causative organisms were group B (4), nonenterococcal group D (3), other groups (2), α-hemolytic nongrouped (3), and nonhemolytic, nongrouped (1).
§In community-acquired meningitis, the causative organisms were anaerobes (3 episodes) and diphtheroids (1); in nosocomial meningitis, the causative organisms were micrococci (2), Neisseria species (1), propionibacteria (1), and diphtheroids (1).

Figure 12-8. Causative organisms of bacterial meningitis. The causative organisms are somewhat different for community-acquired as opposed to nosocomial meningitis. (*Adapted from* Durand *et al*. [5].)

Figure 12-9. Causative organisms of bacterial meningitis by age-related relative frequency. *Haemophilus influenzae* type b was the leading cause of meningitis until widespread use of vaccine. Now *H. influenzae* is not a significant cause of bacterial meningitis in the vaccinated population [6]. Meningococcal meningitis caused by *Neisseria meningitidis* affects mostly children and young adults. As of 1995, *N. meningitidis* had replaced *H. influenzae* as the leading cause of bacterial meningitis in these age groups in the United States [7]. Congenital terminal complement deficiencies (C5-C8) predispose to meningococcemia. Pneumococcal meningitis caused by *Streptococcus pneumoniae* is the most common cause of bacterial meningitis in adults. Predisposing factors include pneumonia, otitis media, sinusitis, head trauma, cerebrospinal fluid leaks, sickle cell disease, splenectomy, diabetes and alcoholism. (*Adapted from* Schuchat *et al*. [8].)

Causative Organisms of Bacterial Meningitis (Percentage of Cases by Age)

Organism	< 1 mo	1–23 mo	2–29 y	30–59 y	≥ 60 y
Haemophilus influenzae	0	0.7	5.4	12.1	2.5
Neisseria meningitidis	0	30.8	59.8	18.2	3.6
Streptococcus pneumoniae	8.7	45.2	27.2	60.6	68.6
Streptococci group D	69.5	19.2	5.4	3	3.6
Listeria monocytogenes	21.8	0	2.2	0.1	21.7

Causative Organisms of Recurrent Meningitis*

Organism	Community-acquired, *n*(%) (*n* = 38)	Nosocomial, *n*(%) (*n* = 41)
Streptococcus pneumoniae	13(34)	1(2)
Gram-negative bacilli†	0	19(46)
Neisseria meningitidis	3(8)	0
Streptococci‡	4(11)	1(2)
Staphylococcus aureus	1(3)	-15
Haemophilus influenzae	4(11)	0
Mixed bacterial species	0	2(5)
Coagulase-negative staphylococci	0	3(7)
Other§	2(5)	1(2)
Culture negative	11(29)	8(20)

**Both initial and recurrent episodes in the 17 patients who had more than one episode of community-acquired meningitis and the 19 patients who had more than one episode of nosocomial meningitis are included. Not included are five patients, each of whom had one episode of community-acquired meningitis and one episode of nosocomial meningitis. The community-acquired episodes in these patients were caused by group A Streptococcus (1), N. meningitidis (1), and S. aureus (1); two episodes were culture negative. The nosocomial episodes were caused by S. aureus (2), Klebsiella (1), and S. pneumoniae (1); one episode was culture negative. Percentages do not total 100 because of rounding.*

†The causative organisms were as follows: Pseudomonas (5 episodes), Klebsiella (4), Enterobacter (3), Acinetobacter (2), Serratia (1), Escherichia coli (1), Proteus (1), Citrobacter (1), and "gram-negative rods" (1).

‡In community-acquired meningitis: α-hemolytic, nongrouped (3 episodes), and group D, not further identified (1); in nosocomial meningitis: nonhemolytic (1).

§In community-acquired meningitis: anaerobes (1 episode) and Campylobacter fetus (1); in nosocomial meningitis: Propionibacterium acnes (1).

Figure 12-10. Causative organisms of recurrent meningitis. *Streptococcus pneumoniae* is the most frequent cause of community-acquired recurrent meningitis. Gram-negative bacilli are the most frequent causes for nosocomial infections. The most frequent risk factors are head trauma, neurosurgical procedures, and cerebrospinal fluid leaks. Other risk factors include immunodeficiencies, immunosuppressant therapy, splenectomy, and parameningeal infection (*eg*, sinusitis, otitis media). (*Adapted from* Durand *et al*. [5].)

Initial Cerebrospinal Fluid Values in 493 Episodes of Bacterial Meningitis*

Variable	Community-acquired, *n*(%) (*n* =296)	Nosocomial, *n*(%) (*n* = 197)
Opening pressure, *mm of water*		
0–139	9	23
140–299	52	52
300–399	20	11
≥ 400	19	15
White cell count per mm^3†		
0–99	10(13)	17(19)
100–4999	61(59)	65(62)
5000–9999	15(15)	11(12)
≥ 10,000	13(13)	7(8)
Percent neutrophils		
0–19	2	2
20–79	19	31
≥ 80	79	66
Total protein, *mg/dL*		
0–45	4	6
46–199	40	42
≥ 200	56	52
Glucose < 40 mg/dL	50	45
Positive Gram stain	60	46
Culture positive	73	83

**The values shown are percentages of all the episodes in which the results of a given study were reported on initial examination of cerebrospinal fluid. Of the 296 community-acquired episodes, opening pressure was reported in 205, the white cell count in 286, percent neutrophils in 271, protein level in 263, glucose level in 269, results of Gram's staining in 272, and culture results in 289. Of the 197 nosocomial episodes, opening pressure was reported in 102, white cell count in 167, percent neutrophils in 163, protein level in 159, glucose level in 164, results of Gram's staining in 126, and culture results in 180. Percentages do not always total 100 because of rounding.*

†Because the data for pleocytosis may be biased by our criteria for culture-negative episodes, the percentages of culture-positive episodes alone are given in parentheses.

Figure 12-11. Cerebrospinal fluid (CSF) abnormalities in acute bacterial meningitis. The characteristic CSF picture in acute bacterial meningitis usually includes an increased opening pressure (greater than 200 mm H_2O); an increased white cell count with a predominance of polymorphonuclear leukocytes or neutrophils; a decreased glucose level (less than 40 mg/dL) or decreased CSF to serum glucose ratio (less than 0.3); and an increased protein level (greater than 45 mg/dL). Turbid CSF seen on visual inspection suggests more than 400 white cells per mm^3. (*Adapted from* Durand *et al*. [5].)

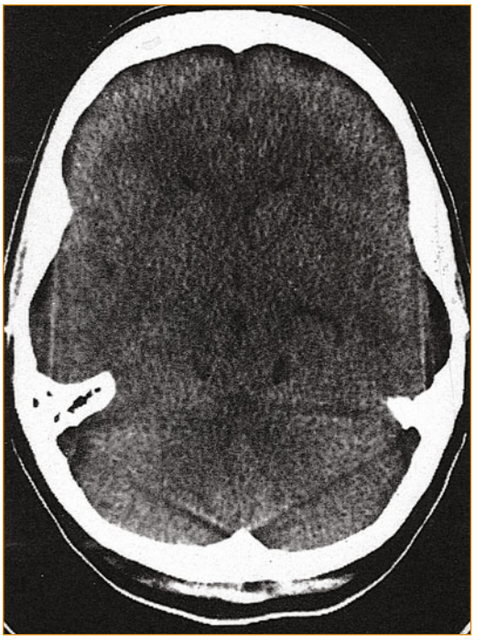


Figure 12-12. CT scan done as part of a diagnostic work-up for acute bacterial meningitis. Diagnostic studies include blood cultures (three sets) and cerebrospinal fluid (CSF) analysis. In addition to routine CSF studies, specialized immunochemical tests should be performed in patients who have been partially treated, even with oral antibiotics. These special tests include latex agglutination, counterimmunoelectrophoresis, limulus amoebocyte lysate, and coagglutination. If the patient shows signs suggestive of increased intracranial pressure (impaired mental status, focal neurologic signs, papilledema, dilated nonreactive pupil, cranial nerve VI palsy), then a brain CT scan should be performed before lumbar puncture (LP). The CT scan may show diffuse cerebral edema (as here) or a focal lesion, which are contraindications to LP. (*From* Roos *et al*. [1]; with permission.)

Figure 12-13. Differential diagnosis of acute bacterial meningitis. Viral meningitis is a diagnostic consideration of very early bacterial meningitis. In viral meningitis, fever is not as prominent, and cerebrospinal fluid (CSF) studies usually reveal normal glucose levels and mononuclear pleocytosis, although polymorphonuclear neutrophils may be seen in the first 12 to 24 hours. In viral encephalitis, the CSF analysis is similar to that of viral meningitis, but mental status is altered. Tuberculous meningitis may be subacute or have a rapid downhill course, but mononuclear cells predominate in the CSF and usually the glucose level is low. Fungal meningitis has a more chronic course. CSF studies reveal a mononuclear pleocytosis and low glucose. Brain abscess and subdural empyema usually present with focal abnormalities on examination, increased intracranial pressure, and a CSF pleocytosis with normal glucose. Rocky Mountain spotted fever may clinically resemble bacterial meningitis, with patients exhibiting fever, headache, altered mental status, and a petechial rash. The rash is usually different than that seen in meningococcemia (*see* Fig. 12-2), beginning on wrists and ankles, then spreading to the body and face; the mucous membranes are not involved. The CSF is usually normal, and a history of tick bite is elicited in 80% of patients. Bacterial endocarditis causes a new heart murmur; petechial lesions of the nailbeds, mucous membranes, and extremities; and hematuria, as well as altered mental status. Subarachnoid hemorrhage presents with sudden, excruciating headache, meningismus, fever at times, usually a normal mental status (unless intracerebral bleeding occurred), and CSF xanthochromia with a large number of red blood cells. Neoplastic meningitis (meningeal carcinomatosis) often causes cranial nerve palsies, mononuclear cells in the CSF, and low glucose levels; the cytologic appearance is diagnostic. A diffuse erythematous maculopapular rash is present in over 50% of patients with meningococcemia. This presents as petechiae and purpura on the trunk and lower extremities (*see* Fig. 12-2). The petechiae may appear on mucous membranes and conjunctivae but never in the nailbeds. Other organisms that cause meningitis less frequently cause similar rashes (*Staphylococcus aureus*, *Acinetobacter* species, *Streptococcus pneumoniae*, and *Haemophilus influenzae*). The rash of staphylococcal endocarditis involves the nailbeds in addition to the mucous membranes and the extremities. Echovirus type 9 infections often also cause a petechial or purpuric rash. EEG—electroencephalogram; FA—fluorescent antibody.

Differential Diagnosis of Bacterial Meningitis

Differential Diagnosis	Diagnostic Test
Viral meningitis	CSF
Viral encephalitis	CSF, EEG, MRI
Tuberculous meningitis	CSF
Fungal meningitis	CSF
Brain abscess	CT
Subdural empyema	CT
Rocky Mountain spotted fever	Rash biopsy with FA staining of specimen
Bacterial endocarditis	Cardiac murmur
Subarachnoid hemorrhage	CSF
Neoplastic meningitis	CSF

Differential Diagnosis in Acute Bacterial Meningitis Based on Typical Cerebrospinal Abnormalities

Type of Infection	Predominant Cells, *per mm³*	Glucose, *mg/dL*	Stain for Organisms	Diagnosis
Bacterial meningitis	PMNs	Very low (0–10)	Gram stain	Culture, CIE, LA, LLA, CoA
Tuberculous meningitis	Mononuclear leukocytes	Low to very low (10–20)	Ziehl-Nelson	Culture, PCR assay
Viral meningitis	Mononuclear leukocytes	Normal		Culture, some PCR assays
Fungal meningitis	Mononuclear leukocytes	Low (15–30)	Cryptococcus—India ink stain	Culture; various Ab and Ag tests
Parameningeal (serous) meningitis	Subacute and chronic: mononuclear leukocytes (usual picture); acute: PMNs (uncommon)	Normal		CT, MRI; myelogram
Neoplastic meningitis	Mononuclear leukocytes	Low or normal (30–50)		Cytologic studies

Figure 12-14. Differential diagnosis of cerebrospinal fluid (CSF) abnormalities in acute bacterial meningitis. Rarely in bacterial meningitis monocytes may predominate in the CSF (*Listeria monocytogenes* and especially brucellosis). In viral meningitis, polymorphonuclear leukocytes (PMNs) may appear in the first 12 to 24 hours, and then there is a shift to mononuclear cells. Most parameningeal foci of infection (*eg*, brain abscess, epidural abscess) cause a subacute to chronic condition of mononuclear cells in the CSF. Subdural empyema, however, may cause an acute parameningeal CSF appearance of a large number of PMNs. Ab—antibody; Ag—antigen; CIE—counter immunoelectrophoresis; CoA—coagglutination; LA—latex agglutination; LLA—limulus lysate assay; PCR—polymerase chain reaction

Empiric Antimicrobial Therapy for Bacterial Meningitis

Population	Antimicrobial Agent
Neonates	Ampicillin plus cefotaxime
Infants and children	Third-generation cephalosporin (cefotaxime or ceftriaxone) plus vancomycin*
Adults (15–50 y)	Third-generation cephalosporin plus vancomycin*
Older adults	Third-generation cephalosporin (ceftriaxone or ceftazidime) plus ampicillin plus vancomycin*
Neurosurgical procedure	Third-generation cephalosporin (ceftazidime) plus vancomycin*
Immunocompromised state	Ampicillin plus third-generation cephalosporin plus vancomycin*
Neutropenic state	Cefepime

**Until susceptibility testing available.*

Figure 12-15. Empiric antimicrobial therapy for acute bacterial meningitis. Empiric antibiotic therapy must be given before the causative organism can be definitively identified. The choice of the empiric agent depends on the patient's age and associated conditions (such as neurosurgical procedure, immunodeficiency), with modifications based on a positive Gram stain. To achieve adequate antibiotic levels in the cerebrospinal fluid, antibiotics should be given intravenously. (*Adapted from* Roos *et al*. [9].)

Antibiotic Therapy for Acute Bacterial Meningitis

Organism	Antibiotics	Organism	Antibiotics
Streptococcus pneumoniae		Enterobacteriaceae	Third-generation cephalosporin*
Sensitive to penicillin	Penicillin G or ampicillin	*Pseudomonas aeruginosa*	Cefepime, meropenem
Relatively resistant to penicillin	Third-generation cephalosporin*	*Streptococcus agalactiae*	Ampicillin or penicillin G§
Resistant to penicillin	Vancomycin plus a third-generation cephalosporin*†‡	*Listeria monocytogenes*	Ampicillin or penicillin G§
Neisseria meningitidis	Penicillin G or ampicillin‡	*Staphylococcus aureus*	
Haemophilus influenzae		Methicillin sensitive	Nafcillin or oxacillin
ß-Lactamase negative	Ampicillin‡	Methicillin resistant	Vancomycin
ß-Lactamase positive	Third-generation cephalosporin*‡	*Staphylococcus epidermidis*	Vancomycin†

**Cefotaxime or ceftriaxone.*
†Addition of rifampin should be considered.
‡Chloramphenicol is an option for penicillin-allergic patients.
§Addition of an aminoglycoside should be considered.

Figure 12-16. Specific antibiotic therapy for acute bacterial meningitis. Once the causative organism is cultured and sensitivities determined, therapy should be adjusted to be as narrow as possible. The duration of treatment is somewhat empiric with the following general recommendations: *Neisseria meningitidis*, 7 days; *Haemophilus influenzae*, 7 to 10 days; *Streptococcus pneumoniae*, 10 to 14 days; gram-negative bacilli, 21 days. (*Adapted from* Roos *et al*. [9].)

Adjunctive Therapy and Supportive Care for Bacterial Meningitis

- Adjunctive dexamethasone: 0.15 mg/kg every 6 h for 4 days for children; 12 mg every 12 h for adults
- Supportive care
  - Fluid and electrolyte balance: monitor for syndrome of inappropriate antidiuretic hormone
  - Maintenance of normal systemic blood pressure because of loss of autoregulation
  - Intracranial pressure (ICP) monitoring for critically ill patients
  - Treatment for increased ICP
    - Elevate head of bed to 30 degrees
    - Hyperventilation to $PaCO_2$ to 27–30 mm Hg
    - Hyperosmolar agents: mannitol, glycerol
    - Glucocorticoids: dexamethasone
  - Monitor and treat obstructive hydrocephalus
  - Seizure control: lorazepam, phenytoin, phenobarbital

Figure 12-17. Adjunctive therapy and supportive care of acute bacterial meningitis. Several studies have demonstrated that dexamethasone decreases sensorineural hearing loss and improves neurologic outcome in children older than 2 months of age [10] as well as adults [11]. The dexamethasone should be started shortly before giving the first dose of antibiotics because the drug inhibits the production of inflammatory cytokines. It appears to be most useful for patients with pneumococcal or meningococcal meningitis. $PaCO_2$—arterial carbon dioxide pressure.

Mortality Rates of Treated Cases of Bacterial Meningitis

		Case Fatality Rate, %	
Organism	**Episodes, *n***	**Meningitis Related, *n***	**Total, *n***
Streptococcus pneumoniae	120	25	28
Gram-negative bacilli	86	23	36
Neisseria meningitidis	40	10	10
Streptococci	36	17	25
Enterococcus	4	25	50
Staphylococcus aureus	36	28	39
Listeria monocytogenes	34	2111	32
Haemophilus influenzae	19	39	11
Mixed bacterial species	18	9	44
Coagulase-negative staphylococci	16	0	0
Other*	12	0	8
Culture negative	72	7	10
All causes	493	19	25
1962–1970	172	21	24
1971–1979	186	18	26
1980–1988	135	17	24

**Other organisms were as follows: anaerobes (4 episodes), propionibacteria (2), diphtheroids (2), micrococci (2), Neisseria species (1), and Campylobacter fetus (1).*

Figure 12-18. Mortality rates of treated cases of acute bacterial meningitis. The mortality rate for treated cases of acute bacterial meningitis remains significant because of the numerous potential complications (increased intracranial pressure, hydrocephalus, focal neurologic deficits, seizures, brain abscess, subdural empyema, sepsis). Factors associated with significantly higher overall mortality rates were age of 60 years or older, obtundation on admission, and seizures occurring within 24 hours of admission. (*Adapted from* Durand *et al*. [5].)

Vaccination for Acute Bacterial Meningitis

Hib Vaccine Recommendations

- Vaccinate all infants at 2, 4, and 6 months of age
  - Unvaccinated infants 7–11 months of age receive two doses 2 months apart
  - Unvaccinated children 12–14 months of age receive one dose plus booster at 15 months
- Unvaccinated children 15–60 months of age receive one dose
- Children older than 5 years are vaccinated if increased disease risk (asplenia, sickle cell disease, immunodeficiency, or immunosuppression)
- Children with history of invasive Hib disease or vaccinated at greater than 2 years with polyribosylribitol phosphate vaccine do not need revaccination

Indicators for Meningococcal and Pneumococcal Vaccines

- Meningococcal quadrivalent vaccine
  - Vaccination during epidemic outbreaks due to represented serogroup
  - Travel to hyperepidemic areas
  - High-risk immunodeficient groups
    - Terminal coagulant deficiency
    - Properdin deficiency
- Pneumococcal vaccine
  - Vaccinate all infants at 2, 4, and 6 months of age
  - Elderly over 65 years of age
  - Those with chronic cardiorespiratory conditions
  - Chronic alcoholics
  - Those with asplenic states, multiple myelemia, Wiskott-Aldrich syndrome
  - HIV infection
  - Those with diabetes mellitus or significant hepatic or renal disease

Figure 12-19. Vaccination for acute bacterial meningitis. Vaccines are now available for *Haemophilus influenzae* type b (Hib), *Neisseria meningitides*, and *Streptococcus pneumoniae*. The routine use of Hib vaccine has greatly decreased the incidence of meningitis due to this agent [12]. Meningococcal and pneumococcal vaccines are used for specific circumstances or "at risk" populations. Meningococcal vaccine is available for serogroups A, C, Y, and W135 (quadrivalent vaccine), but the response is poor in young children, and there is no vaccine for serogroup B, which is responsible for over 50% of infections in the United States [13]. Pneumococcal vaccine is indicated for all infants in addition to high-risk groups older than 2 years of age [12]. It is recommended that close household, day care center, and medical personnel contacts for meningococcal and *H. influenzae* meningitis be treated prophylactically with rifampin.

Chronic Bacterial Meningitis

Differential Diagnosis of Chronic Meningitis

Infectious Causes

- Bacterial infections
  - Tuberculosis
  - Spirochetal (syphilis, Lyme disease, Leptospira infection)
  - Agents that form sinus tracts *(Actinomyces, Arachnia, Nocardia)*
  - Brucellosis
  - *Listeria monocytogenes* (rare cause)
  - Nocardiosis
- Fungal infections
  - Common *(Candida, Coccidioides, Cryptococcus, Histoplasma)*
  - Uncommon *(Aspergillus, Blastomyces, Dematiaceous paracoccidioides, Pseudallescheria, Sporothrix, Mucormycetes)*
- Parasitic diseases
  - Cysticercosis
  - Granulomatous amebic meningoencephalitis (acanthamoeba)
  - Eosinophilic meningitis (angiostrongylus)
  - Toxoplasmosis
  - *Coenurus cerebralis*
- Viral infections
  - Retrovirus (HIV-1, HTLV-1)
  - Enterovirus (in hypogammaglobulinemia)
- Parameningeal infections (epidural abscess, subdural empyema, brain abscess)

Noninfectious Causes

- Neoplasm
- Sarcoidosis
- Vasculitis
  - Primary central nervous system angiitis
  - Systemic: giant cell arteritis, systemic lupus erythematosus, Sjögren's syndrome, rheumatoid arthritis, lymphamatoid granulomatosis, polyarteritis nodosa, Wegener's granulomatosis)
- Behçet's disease
- Chemical meningitis
  - Endogenous
  - Exogenous
- Chronic benign lymphocytic meningitis
- Idiopathic hypertrophic pachymeningitis
- Vogt-Koyanagi-Harada disease

Figure 12-20. Differential diagnosis of chronic meningitis. Chronic meningitis accounts for about 10% of all meningitis cases. Clinical features include a subacute to chronic onset of various combinations of fever, headache, and stiff neck, often with signs of encephalitis (parenchymal involvement), mental status changes, seizures, and focal deficits. Therefore, chronic meningitis is often referred to as a meningoencephalitis. The cerebrospinal fluid (CSF) is abnormal with a pleocytosis (usually mononuclear), elevated protein levels, and a moderately decreased glucose level (*see* Fig. 12-14 for comparison). Some require that these manifestations persist for 4 weeks as a criterion for the diagnosis of chronic meningitis; however, the differential diagnosis is usually considered before this period on the basis of the suggestive CSF profile. The differential diagnosis is quite extensive and includes both infectious and noninfectious causes. The most common infectious causes of chronic meningitis are tuberculosis, cryptococcosis, and toxoplasmosis; the common noninfectious causes are neoplasms and vasculitis. HTLV—human T-cell lymphotropic virus. (*Adapted from* Roos and Bonnin [2].)

Historical and Clinical Clues to Diagnosis of Chronic Meningitis

History

- Exposure history
  - To patient with tuberculosis (TB)
  - Ingestion of unpasteurized milk or dairy products (brucellosis)
  - To farm animals or swimming in farm ponds (leptospirosis)
  - To deer ticks (Lyme disease)
  - Swimming in warm fresh water ponds (acanthamebiasis)
  - Sexual transmission (syphilis, retroviruses)
  - Intravenous drug use (retroviruses)
- Travel and geographic history
  - Mexico and Latin America (cysticercosis)
  - Southeast Asia and Pacific (angiostrongylosis)
  - US Northeast, North Central (Lyme disease)
  - US Midwest (histoplasmosis, blastomycosis)
  - US Southwest (coccidioidomycosis)
  - US Southeast (acanthamebiasis)
- History of extraneural or systemic disease
  - Pulmonary disease (TB, histoplasmosis, sarcoidosis)
  - Polyarthritis (Lyme disease, Behçet's syndrome, systemic lupus erythematosus, rheumatoid arthritis)
  - Uveitis (sarcoidosis, Behçet's syndrome, Vogt-Koyanagi-Harada [VKH, leptospirosis)
  - Skin lesions (syphilis, Lyme disease, VKH)
  - Prior diagnosed disease (diabetes, malignancy, TB, syphilis, AIDS)
- History of immunodeficiency
  - Congenital
    - Agammaglobulinemia (enteroviruses)
  - Acquired
    - AIDS (toxoplasmosis, cryptococcosis, syphilis, TB, etc.)
    - Organ transplant immunosuppression (toxoplasmosis, listeriosis, candidiasis, nocardiosis, aspergillosis)
    - Chronic steroid use (TB, cryptococcosis, candidiasis)
    - Malignancy and chemotherapy (TB, cryptococcosis, listeriosis)

Examination

- Dermatologic lesions
  - Erythema chronicum migrans—Lyme disease
  - Depigmentation of skin (vitiligo) and hair (poliosis)—VKH
  - Macular hyperpigmented lesions of trunk, palms, and soles—secondary syphilis
  - Subcutaneous nodules, abscesses, draining sinuses—fungal aspergillosis
- Ophthalmologic disease
  - Uveitis—sarcoidosis, Behçet's syndrome, VKH
  - Choroidal tubercles—TB, sarcoidosis
- Organ disease
  - Primary disease—sarcoidosis, TB, histoplasmosis, aspergillosis, blastomycosis
  - Enlarged liver—potential biopsy sites for TB, histoplasmosis
  - Muscle nodules—biopsy site for sarcoidosis, vasculitis
  - Adenopathy—biopsy site for TB, systemic fungi
- Neurologic features
  - Cranial nerve involvement—sarcoidosis, Lyme disease, TB, fungal meningitis
- Focal lesions
  - Abscess—TB, fungal meningitis, toxoplasmosis
  - Strokes—TB, aspergillosis, mucormycosis, vasculitis
- Hydrocephalus—TB, fungal meningitis, especially cryptococcosis, cystinosis
- Peripheral neuropathy—Lyme disease, sarcoidosis, brucellosis, vasculitis
- Multiple levels—carcinomatous meningitis

Figure 12-21. Historical and examination clues to chronic meningitis. Exploring the history may reveal clues to an etiologic diagnosis, although unfortunately such a clue is not found in most cases, which does not exclude any of the possible diagnoses. The history can be explored in four major areas: exposure history, travel and geographic history, extraneural or systemic diseases, and immunologic deficiency. The physical examination of patients with chronic meningitis is directed at finding extraneural signs that provide clues to the central nervous system disease, identifying potential sites for biopsy, and documenting the exact location and extent of neurologic involvement. For example, skin and eye involvement support specific diagnoses, and skin, adenopathy, and organomegaly indicate potential biopsy sites. (*Adapted from* Roos and Bonnin [2].)

Laboratory Tests in Chronic Meningitis

- Blood tests: CBC, serum chemistry studies, ANA, ANCA, ESR, VDRL, ACE
- Cultures of draining skin lesions, sinuses, nodes, blood, sputum, urine, CSF
  - Multiple sites
  - Multiple times (≥ 3)
- Skin testing
  - Intermediate PPD
  - Anergy battery
- Antibody studies
  - Paired serum and CSF samples
- CSF studies (× 3 if needed)
  - Cells, protein, glucose, antigen assays (fungus only), antibody assays, culture, cytologic analyses (Gram stain, India ink preparations, acid-fast stains), PCR assays
- Imaging
  - Chest radiography
  - Contrast-enhanced MRI preferred over CT
  - Angiography
- Biopsy
  - Extraneural
  - Meningeal/cerebral

Figure 12-22. Laboratory tests in chronic meningitis. A complete blood count (CBC) may reveal bone marrow disease (tuberculosis [TB], vasculitis, neoplasms). Abnormal results of serum chemistry tests may include a low sodium level (syndrome of inappropriate antidiuretic hormone from TB); a high sodium level from diabetes insipidus (sarcoid); high levels of calcium and angiotensin-converting enzyme (ACE) (sarcoid); elevated liver function tests (TB, sarcoid, histoplasmosis); and positive antinuclear antibodies (ANA) and antineutrophil cytoplasmic antibodies (ANCA) (systemic vasculitis). Cerebrospinal fluid (CSF) examination is the most important test for the diagnosis of chronic meningitis. If several lumbar CSF studies have negative results, then cisternal or lateral cervical CSF studies are needed, because basilar meningitis commonly occurs with chronic meningeal processes. A ventricular tap for CSF may ultimately be necessary. Chest radiographs are needed to determine the presence of TB, sarcoid, histoplasmosis, or tumor. Brain imaging studies should be performed before a spinal tap to exclude focal brain lesions (abscess or stroke) and hydrocephalus. Enhancements help to localize abscesses as well as reveal chronic meningeal inflammation. MRI is needed for spinal disease. Angiography may be useful for diagnosing systemic or central nervous system vasculitis. If these tests are not diagnostic, then biopsies may be required, especially if the patient continues to deteriorate. ESR—erythrocyte sedimentation rate; PCR—polymerase chain reaction; PPD—purified protein derivative; VDRL—Venereal Disease Research Laboratory test.

CSF Finding in Diagnosis of Chronic Meningitis

Type of Pleocytosis	Noninfectious Meningitis (Usually < 50 cells/mL)
Mononuclear cells with low glucose levels	Neoplastic meningitis
	Sarcoid
	Tuberculosis meningitis
	Fungal meningitis
	Syphilis
	Lyme disease
	Cysticercosis
	Toxoplasmosis
Mononuclear cells with normal glucose levels	Neoplastic meningitis
	Sarcoid
	Lyme disease
	Vasculitis
	Parameningeal infection
	Chronic benign lymphocytic meningitis
	Chemical meningitis
Neutrophilic predominance	Bacterial infection (*Actinomyces, Brucella, Nocardia*, early TB)
	Fungal infection (*Aspergillus, Blastomyces, Candida, Coccidioides, Histoplasma, Pseudallescheria, Mucormycetes*)
	Noninfectious meningitis (chemical, vasculitis)
Eosinophilic predominance	Parasitic infection (*Angiostrongylus*, cysticercus, *Gnathostoma*)
	Bacterial infection (*Coccidioides*)
	Noninfectious meningitis (vasculitis, chemical)
	Neoplastic meningitis (lymphomatous, Hodgkin's disease)

Figure 12-23. Cerebrospinal fluid (CSF) finding in differential diagnosis of chronic meningitis. In the CSF, the cellular infiltrate is mononuclear for most causes of chronic meningitis. The glucose is low or normal. However, there are a few chronic infections that predominately have a neutrophilic response, which is the type of response usually seen in acute infections. Also, a few organisms elicit allergic eosinophilic responses. TB—tuberculosis.

Clinical Staging of Tuberculous Meningitis

Stage I (early)	Nonspecific symptoms and signs
	No clouding of consciousness
	No neurologic deficits
Stage II (intermediate)	Lethargy or alteration in behavior
	Meningeal irritation
	Minor neurologic deficits
	(such as cranial nerve palsies)
Stage III (advanced)	Abnormal movements
	Convulsions
	Stupor or coma
	Severe neurologic deficits (pareses)

Figure 12-24. Clinical staging of tuberculous meningitis. Because the clinical picture of meningitis due to tuberculosis varies, especially by age at onset, a clinical staging system was introduced 50 years ago. Stage I patients have only a nonspecific prodrome without neurologic manifestations, which includes headache, malaise, and low-grade fever. This stage usually lasts up to 2 weeks. Stage II is often referred to as the meningitic phase, as symptoms and signs of meningitis occur along with cranial nerve palsies. Behavior alteration and lethargy may be seen. This stage progresses over days to weeks to stage III (advanced), in which seizures, stupor or coma, focal neurologic signs, and decorticate or decerebrate posturing occur. Without treatment, the course proceeds steadily downhill to death in 6 to 12 weeks. Disease progression tends to occur faster in adults. Rarely, other forms of tuberculous meningitis may be seen. It can present acutely, similar to acute bacterial meningitis, with a more rapid course. Infrequently, it has a more chronic course, with slowly developing hydrocephalus, similar to fungal meningitis. A stroke syndrome has also been associated with tuberculous meningitis. (*Adapted from* the British Medical Research Council [14].)

Symptoms and Signs of Tuberculous Meningitis at Presentation

Manifestations	Children, %	Adults, %
Symptoms		
Headache	20–50	50–60
Nausea/vomiting	50–75	8–40
Apathy/behavioral changes	30–70	30–70
Seizures	10–20	0–13
Prior history of tuberculosis	55	8–12
Signs		
Fever	50–100	60–100
Meningismus	70–100	60–70
Cranial nerve palsy	15–30	15–40
Coma/altered consciousness	30–45	20–30
Purified protein derivative-positive	85–90	40–65

Figure 12-25. Symptoms and signs of tuberculous meningitis at presentation. The clinical presentation in children is somewhat different than that seen in adults. Nausea and vomiting as well as behavioral changes are more common in children, whereas headache is clearly more common in adults. Children also frequently complain of abdominal pain and constipation. In both groups, seizures increase in frequency with disease progression. On examination, fever and meningismus are the most common signs in both age groups, although the frequency varies greatly. Cranial nerve palsies are present in some patients at presentation but eventually occur in about half of all cases. The sixth cranial nerve is involved most commonly, followed by the third, fourth, and seventh cranial nerves. Examination of the optic fundus may reveal tubercles in a small percentage of patients. Funduscopic examination may also reveal papilledema due to increased intracranial pressure from hydrocephalus. Hydrocephalus correlates well with the duration of disease and eventually occurs in most cases.

Additional manifestations of central nervous system tuberculosis include the following discussed below. Caseating granulomas of epithelioid cells and macrophages containing mycobacteria may occur in the brain as single or multiple focal lesions. Infrequently, caseating necrosis occurs, forming a tuberculous (cold) abscess. Both lesions often occur without meningitis. Most often, the initial presentation of tuberculoma and abscess is similar to that of a brain tumor, with headaches from increased intracranial pressure, seizures, focal deficits, and altered mental status. Less frequently, seizure or focal deficits may be the first manifestations. The most common form of tuberculosis of the spine is epidural compression of the thoracic cord from vertebral and disc destruction by caseating granulomas (tuberculous osteomyelitis). Less frequently the lumbar or cervical spine may be affected. The clinical manifestations are those of chronic epidural cord compression with back pain increased with weight bearing; percussion tenderness over the spine; a spastic paraparesis, often with a sensory level; and bowel and bladder dysfunction. Localized and severe percussion spine tenderness with painful limitation of spinal motility is referred to as a "spinal gibbus." Tuberculous meningomyelitis is the rare occurrence of infection of the spinal leptomeninges without spine involvement; it has also been referred to as spinal meningitis, spinal arachnoiditis, and spinal radiculomyelitis. Thick exudates and tubercles encase the nerve roots and spinal cord. This process presents as subacute to chronic radiculomyelitis or as cauda equina syndrome. It appears mainly in highly endemic areas but has been reported in AIDS patients in the United States. Intramedullary tuberculomas are rare and have clinical presentations similar to other spinal cord tumors. (*Adapted from* Zuger and Lowy [15].)

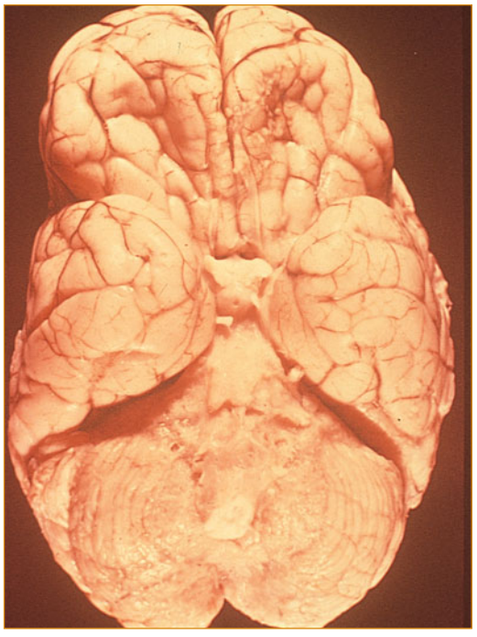


Figure 12-26. Tuberculous basilar meningitis. The tubercle bacillus enters the human host through inhalation. Airborne droplets reach the alveoli and multiply there or in alveolar and circulating macrophages. During this 2- to 4-week stage of infection, hematogenous dissemination occurs, and delayed secondary hematogenous dissemination may also occur. During dissemination, tubercles form in multiple organs, including the brain. Eventually tubercles rupture into the subarachnoid space or ventricular system to cause meningitis.

The initial pathologic event after tubercle rupture is the formation of a thick exudate in the subarachnoid space. This exudate initially begins at the base of the brain, where it is especially thick, and envelops cranial nerves, causing cranial nerve palsies. (*From* Wilson [4]; with permission.)

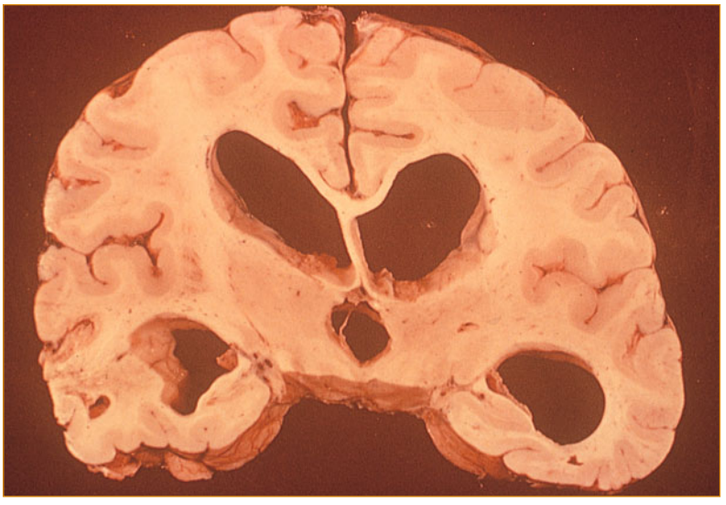


Figure 12-27. Tuberculous hydrocephalus. With the thick basilar exudate of tuberculous meningitis, often the foramina of Luschka and Magendie become obstructed. Obstruction may also occur at the level of the aqueduct, causing noncommunicating hydrocephalus, increased intracranial pressure, and papilledema. Communicating hydrocephalus caused by blockage of the basilar cisterns, interfering with the resorption of cerebrospinal fluid, may also occur. Either type of hydrocephalus may result in brain atrophy. (*From* Wilson [4]; with permission.)

Prevalence of CNS Tuberculosis in AIDS Patients

Location	Year	Cases of Active TB/ Cases of AIDS	Cases of TB with CNS Disease
Florida	1984	27/45 (60%)	2 of 27 (7%)
New Jersey	1986	52/420 (12%)	10 of 52 (19%)
New York City	1986	24/280 (9%)	1 of 24 (4%)
San Francisco	1987	35/1705 (2%)	2 of 35 (6%)
Barcelona, Spain	1988	Not available	5 of 65 (8%)

Figure 12-28. Prevalence of tuberculosis (TB) of the central nervous system (CNS) in AIDS patients. In the first half of the 20th century, autopsy studies revealed that 5% to 10% of patients with TB had CNS involvement. TB in AIDS patients is thought to occur because of reactivation; most cases are pulmonary, but the incidence of extrapulmonary disease is much greater than that of the general population. Rates of tuberculin purified protein derivative reactivity are lower than those in the general population, ranging from 33% to 50% as compared to 50% to 90%. The incidence of CNS involvement is similar to that of the general population. (*Adapted from* Zuger and Lowy [15].)

Laboratory Diagnosis of Tuberculous Meningitis

Test	Positivity, %	Problems
CSF lymphocytic pleocytosis with decreased glucose	~75	Nonspecific
AFB CSF staining	~32	Low sensitivity
		Microscopic time dependent
CSF culture	~50	Low sensitivity
		Too long for early diagnosis
CSF adenosine deaminase	~75	Low specificity
		Not always available
PCR	50–98	Depends on sequence amplified
Tuberculin skin test	Adults 40–65	Low sensitivity in adults
	Children 85–90	
Chest radiograph	Adults 25–50	Low sensitivity
	Children 15–20	
CSF imaging (CT or MRI)	75–85	Nonspecific

Figure 12-29. The laboratory diagnosis of tuberculous meningitis is difficult. Routine cerebrospinal fluid (CSF) parameters (lymphocytic pleocytosis and low glucose), CSF adenosine deaminase, and CSF imaging are nonspecific. Acid fast bacilli (AFB) staining, CSF culture, tuberculin skin test, and chest radiograph have low sensitivity. CSF culture is specific but takes too long for needed early diagnosis. Polymerase chain reaction (PCR) sequence amplification has the greatest sensitivity, depending on which sequence is amplified. (*Adapted from* Zuger [16] and Rafi *et al*. [17].)

Recommended Treatment Regimen for Tuberculous Meningitis from The American Thoracic Society, Centers for Disease Control and Prevention, and The Infectious Diseases Society of America, 2003

	Initial Regimen		Subsequent Regimen	
	Drug	Duration	Drug	Duration
Low suspicion of drug resistance	Isoniazid	2 mo	Isoniazid	7–10 mo
	Rifampin	2 mo	Rifampin	7–10 mo
	Pyrazinamide	2 mo		
	Ethambutol	2 mo		
	Dexamethasone*	6 wk		
High suspicion of drug resistance	In consultation with a specialist, begin treatment with at least three previously unused drugs to which in vitro susceptibility is likely. Depending on resistance pattern, treatment may have to continue for up to 24 mo.			

**Recommended dose: 8 mg/d for children < 25 kg and 12 mg/d for children > 25 kg and adults for 3 wks, then tapered over the next 3 wks.*

Figure 12-30. Chemotherapeutic options for tuberculous meningitis have been extrapolated from the treatment of other forms of tuberculosis (TB). Because of the rarity of tuberculous meningitis in developed countries, questions related to the optimal regimen, doses, routes of administration, and length of treatment have not been clarified. The number of drugs used depends on the probability of drug resistance. Most drug-resistant cases in the United States occur in AIDS patients and prisoners. Antituberculous chemotherapy must be initiated as soon as tuberculous meningitis is suspected based upon the cerebrospinal fluid formula. Delays in treatment due to waiting for positive results from smears or cultures usually result in increased mortality and morbidity. Corticosteroids (dexamethasone) are now recommended as standard treatment. Other adjunctive therapy includes ventricular drainage for hydrocephalus. Tuberculomas presenting with acute swelling and edema (TB brain abscess) should also be treated with steroids, in which case surgical removal may be required [18].

Paradoxical responses to treatment have been reported up to 1 year during chemotherapy. It is defined as clinical or radiological worsening of pre-existing TB lesions (TB developing abscess formation or enlarging) or the development of new lesions. Treatment is with steroids with or without surgical intervention [19]. (*Adapted from* American Thoracic Society [18].)

Mortality Rates for Tuberculous Meningitis

Age	Percent	Duration of Symptoms	Percent	Stage	Percent
< 5 y	20	0–2 m	9	Stage I	0
5–50 y	8	> 2 m	80	Stage II	10
> 50 y	60			Stage III	45

Figure 12-31. Mortality and morbidity rates of tuberculous meningitis. Mortality and morbidity rates depend on several factors, including the patient's age, the duration of symptoms, and the stage of the disease. (*Adapted from* Kennedy and Fallon [20].)

Clinical Manifestations and Pathogenesis of Intracranial Epidural Abscess

Clinical Manifestations	Sources of Infection
Early	Extension of contiguous infections
Fever	Paranasal sinusitis
Symptoms related to the source of infection	Orbital cellulitis
Sinusitis, otitis, etc.	Otitis
Headache	Mastoiditis
Localized skull tenderness from osteomyelitis	Cranial defects
Scalp and face cellulitis from osteomyelitis	Skull fracture
Cranial nerve palsies—rare	Neurosurgic procedures
Late	
Seizures	
Focal neurologic deficits	
Meningismus	
Nausea and vomiting from increase ICP	
Papilledema from increased ICP	
Altered mental status from increased ICP	
Cranial nerve palsies—rare	

Figure 12-32. Clinical manifestations and pathogenesis of intracranial epidural abscess. An intracranial epidural abscess is a localized area of infection between the skull and dura caused by the spread of infection from contiguous locations, such as the paranasal sinuses, the ear, and the orbit or because of skull defects. Because the abscess grows by pushing the dura away from the skull, the process is slow and the lesion well circumscribed. Osteomyelitis of the skull may accompany the process, causing swelling and edema of the scalp and face, and skull tenderness. Because the abscess grows slowly, seizures, focal neurologic deficits, and an altered level of consciousness with increased intracranial pressure (ICP) occur late in the course. Cranial nerve palsies are uncommon, but may occur from increased ICP or when the abscess involves sites in which cranial nerves penetrate the dura. Infection of the apex of the petrous temporal bone may involve cranial nerves V and VI, causing facial pain, sensory loss, and lateral rectus palsy ("Gradenigo's syndrome"). Complications from the spread of infection include dural sinus or cortical vein thrombosis with infarction, subdural empyema, meningitis, and brain abscess.

Organisms Commonly Causing Intracranial Epidural Abscess (by Location of Primary Infection)

Paranasal sinuses	Otitis media	Cranial trauma or surgery
Hemolytic streptococci	*Streptococcus pneumoniae*	Staphylococci
Microaerophilic streptococci	*Haemophilus influenzae*	Streptococcal pneumonia
Gram-negative aerobes	Hemolytic streptococci	
Bacteroides or other anaerobes	Gram-negative aerobes	
Rhinocerebral mucormycosis (in diabetic or immunosuppressed patients)		

Figure 12-33. Etiology of intracranial epidural abscess. The responsible organisms are those commonly associated with the primary infectious process. Cranial epidural abscess is rare in young children, occurring mainly in adolescents and adults. The exact incidence of intracranial abscess is not known, but it is much less common than subdural empyema and brain abscess.

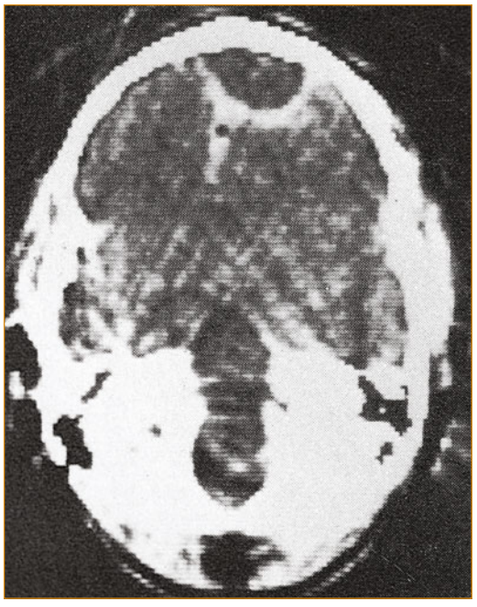


Figure 12-34. CT scan of an epidural abscess revealing a lesion that is well-localized, extracerebral, hypodense, and lenticularly shaped, with a nonenhancing hyperdense medial capsule. Diagnosis of intracranial epidural abscess is made by CT or MRI. Even if the initial CT is not diagnostic, contrast-enhanced MRI scanning should clarify the diagnosis. The cerebrospinal fluid usually reveals a picture of a chronic parameningeal focus with mononuclear pleocytosis, normal glucose levels, and sterile cultures. Differential diagnoses include epidural tumor, epidural hematoma, subdural hemorrhage, subdural empyema, dural sinus or cortical vein thrombosis, and less frequently, brain abscess or brain tumor. (*From* Weisberg *et al*. [21]; with permission.)

Treatment of Intracranial Epidural Abscess

- Empiric antibiotic therapy
  - Paranasal sinus or otitis source of infection
    - Ceftriaxone plus metronidazole
  - Cranial trauma or surgery
    - Vancomycin plus ceftazidime (or plus meropenem)
- Surgical drainage and decompression
  - Gram stain and culture for bacteria and fungi
  - Craniectomy for osteomyelitis
  - Dural debridement; excision and grafting not usually required
  - Closure of any communication between sinus cavity and epidural space to prevent reaccumulation
- Institute specific antibiotic therapy based on culture results

Figure 12-35. Treatment of intracranial epidural abscess. Therapy for intracranial epidural abscess consists of antibiotic therapy combined with neurosurgical drainage and decompression. Antibiotic therapy should be continued for 4 to 6 weeks and for 8 weeks with associated osteomyelitis. The prognosis for these epidural infections is excellent, with no mortality in recent series, probably because the process is usually subacute to chronic and CT and MRI are excellent diagnostic tools.

Spinal Epidural Abscess

Clinical Stages of Progression of Spinal Epidural Abscess

Stage I	Severe localized back pain
	Exquisite spinal percussion tenderness
	Paraspinal muscle spasm
Stage II	Nerve root irritation with radiating pain and paresthesia (radiculopathy)
	Focal weakness or reflex changes
Stage III	Spinal cord compression, with
	Progressive weakness
	Sensory loss
	Bowel and bladder dysfunction
Stage IV	Complete paralysis
	Sensation is impaired below sensory level at or near the cord segment of the lesion

Figure 12-36. Clinical manifestations of spinal epidural abscess by stages of progression. The epidural space in the spinal cord is a true space, unlike the potential epidural intracranial space. In the spinal cord, the dura and arachnoid are closely approximated, so that the subdural space is only a potential space, and spinal subdural empyema or abscess is rare; spinal epidural abscess is much more common. Spinal epidural abscess is an emergency because spinal cord compression and paraplegia are possible rapid complications that can occur over hours. It can be acute (symptoms are present less than 2 weeks) or chronic (symptoms are present for more than 2 weeks); the acute form is more common. Four stages of progression of spinal epidural abscess have been recognized. The acute form presents as an acute cord compression. Progression from stages I to II and from stages II to III usually takes 1 to 4 days each. Once stage III is reached, complete paralysis may occur in hours. In the acute form fever, malaise, and a "flu-like" prodrome may occur. The chronic form presents as an expanding tumor, usually without fever or other prodromal symptoms.

A **Pathogenesis and Pathophysiology of Spinal Epidural Abscess: Location of Spinal Epidural Abscess**

Location	Patients, *n (%)*
Cervical	20 (14)
Thoracic	71 (51)
Lumbar	48 (35)
	Total: 139 (100)
Anterior	28 (21)
Posterior	105 (79)
	Total: 133 (100)

B **Pathogenesis and Pathophysiology of Spinal Epidural Abscess: Source of Infection of Spinal Epidural Abscess**

Source	Percentage of Patients*
Hematogenous seeding	43
Skin and soft tissues	20
Abdomen and pelvis	7
Respiratory system	6
Intravenous drug use	5
Urinary tract	2
Cardiac system	2
Dental infection	1
Contiguous location	27
Vertebral osteomyelitis	8
Retroperitoneal or retromediastinal infection	7
Perinephric or psoas abscess	8
Decubitis ulcers	4
Surgery and trauma	5
No source identified	25
Total	100

**Estimates compiled from various series.*

Figure 12-37. Pathogenesis and pathophysiology of spinal epidural abscess. **A**, Locations of spinal epidural abscess. Spinal epidural abscesses tend to occur most frequently in the thoracic and lumbar levels, posterior to the cord where the epidural space is largest and contains more epidural fat. **B**, Source of infection of spinal epidural abscess. Hematogenous or metastatic seeding is the most common source of infection, occurring from cutaneous, respiratory, abdominal, pelvic, urinary, cardiac, and dental sites of infection as well as from intravenous drug use. Hematogenous seeding is most likely to occur in the thoracic area owing to the end-anastomotic blood supply in this area. Contiguous sources of infection include vertebral body osteomyelitis and retroperitoneal and perinephric infections. Trauma and surgery (back surgery, epidural catheterization for anesthesia and pain control, dorsal column stimulators, lumbar puncture) play a lesser role. Medical conditions associated with spinal epidural abscess include diabetes, malignancy, cirrhosis, renal failure, and alcoholism. By far the most common etiologic agent is *Staphylococcus aureus*, although gram-negative aerobic bacilli (especially *Escherichia coli* and *Pseudomonas* species) have accounted for an increasing percentage of cases. In addition, tuberculosis has accounted for up to 25% of cases in recent series. (*Adapted from* Danner and Hartman [22].)

Diagnosis

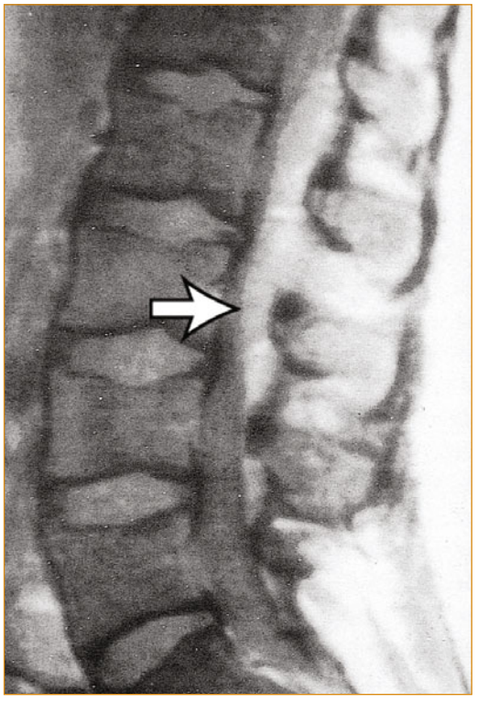


Figure 12-38. Contrast-enhanced T1-weighted MRI done as part of a diagnostic work-up for spinal epidural abscess. This scan reveals an epidural mass (*arrow*) extending from the lower part of the L1 vertebral body to the upper part of the L4 vertebral body. Patients with acute spinal epidural abscess have a high peripheral leukocytic count from 12,000 to 15,000 cells per mm^3. If the process is chronic, the peripheral leukocyte count may be normal. Cerebrospinal fluid (CSF) examination is consistent with parameningeal infection, with an elevated cell count, elevated protein level, normal glucose level, and negative cultures. When the process is acute, usually polymorphonuclear leukocytes predominate, with up to 100 to 200 cells per mm^3; in chronic cases, mononuclear cells predominate, usually with fewer than 50 cells per mm^3. CSF cultures are negative unless the organism has spread to the CSF and subsequently caused meningitis. Blood cultures are positive 60% to 70% of the time. The definitive diagnostic studies, however, are CT myelograms and MRI scans, with MRI the study of choice. MRI scans directly visualize the extent of the abscess and should include T1-weighted images before and after contrast enhancement and a T2-weighted image.

Treatment usually consists of surgical decompression, abscess drainage, and parenteral antibiotics. Empirical treatment is with a combination of a third-generation cephalosporin (*eg*, ceftriaxone) with another antibiotic for methicillin-resistant staphylococci (vancomycin). Once the etiologic bacteria have been identified, the antibiotic regimen should be adjusted based on sensitivities. Antibiotic treatment should continue for at least 4 weeks and 8 weeks with osteomyelitis. Corticosteroids have been used for cord compression, but their benefit has not been subjected to controlled studies. (*From* Gelfand *et al*. [23]; with permission.)

Intracranial Subdural Empyema

Clinical Manifestations of Subdural Empyema

Signs/symptoms	Patients, *n**	Percentage
Fever	420	77
Headache	467	74
Hemiparesis	389	71
Altered consciousness	544	69
Nuchal rigidity	385	63
Seizures	576	48
Papilledema	238	33
Altered speech	364	22
Other focal deficits	265	45

**Total number of patients assessed for the specific manifestation.*

Figure 12-39. Clinical manifestations of intracranial subdural empyema. Subdural empyema is a fulminant, purulent infection that spreads over the cerebral hemispheres in the existing subdural space. It is usually confined to one side of the brain by the anatomic barriers of the falx and tentorium. Undiagnosed and untreated, subdural empyema is rapidly fatal and therefore is a neurologic emergency. Usually patients have a nonspecific prodrome for several days to a week and then become acutely ill. After head trauma or surgery, the presentation may be milder and more subacute. The presenting manifestations usually include fever, headache, hemiparesis, nuchal rigidity, and seizures. As the process continues, increased intracranial pressure causes papilledema and alteration of consciousness. At the end of the first week and into the second, cortical vein thrombosis begins to occur, causing infarcts and additional focal deficits. (*Adapted from* Hartman *et al*. [24].)

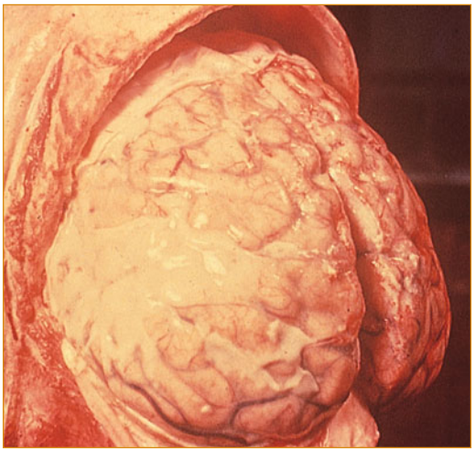


Figure 12-40. Pathologic specimen showing acute subdural empyema with large amounts of exudate overlying parts of the left cerebral hemisphere. The exudate is usually grey or yellowish. The histologic findings in subdural empyema are typical of acute inflammatory processes: the exudate is composed primarily of polymorphonuclear leukocytes, although a few lymphocytes and plasma cells may be present. (*From* Wilson [4]; with permission.)

Etiology of Adult Subdural Empyema

Organism	Incidence*, %
Streptococci	
Aerobic†	36
Anaerobic	10
Staphylococci	
Coagulase-positive	9
Coagulase-negative	3
Aerobic gram-negative bacilli‡	10
Other anaerobes	6
Sterile	29

**394 evaluated cases, total greater than 100% because of multiple isolates from single cases.*
†Includes α-hemolytic, β-hemolytic, and nonhemolytic.
‡Mostly enteric bacilli.

Figure 12-41. Predisposing causes, pathogenesis, and etiology of subdural empyema. The vast majority of cases of subdural empyema occur in males (about 75%). It has been suggested that this is related to the growth of the frontal sinuses in boys during puberty. The most common predisposing cause of subdural empyema is sinusitis (54%). After infection has started in the sinuses, the middle ear, or other areas of the head, it spreads to the subdural space by means of venous drainage. Emissary veins connect the large veins of the scalp and face with the dural venous sinuses, and because the veins of the head and brain are valveless, retrograde spread of thrombophlebitis into the dural and cortical veins from infected venous sinuses may occur. The frontal sinus is probably the single most predisposing site of infection; the incidence of subdural empyema following frontal sinusitis is 1% to 2%. Another predisposing cause of subdural empyema is infection and trauma of the head (about 13%). This is followed by otogenic infections (otitis, mastoiditis—about 13%), which may also spread to the subdural space by erosion of bone. Otogenic infections usually cause a posterior fossa (infratentorial) subdural empyema; about 10% of all cases are infratentorial. A minor predisposing cause of subdural empyema is hematogenous spread (about 3%). Most cases of subdural empyema occur during the second decade of life (about 40%), followed by the third (about 15%), first (about 11%), fourth (about 10%), and fifth (about 9%) decades. Streptococci and staphylococci are the most common causative organisms. Sinus and ear infections usually result in streptococcal subdural empyema, while head trauma or surgery usually results in a staphylococcal subdural empyema. Meningitis is an important predisposing condition in infants but not in adults. (*Adapted from* Hartman *et al*. [24].)

Diagnosis

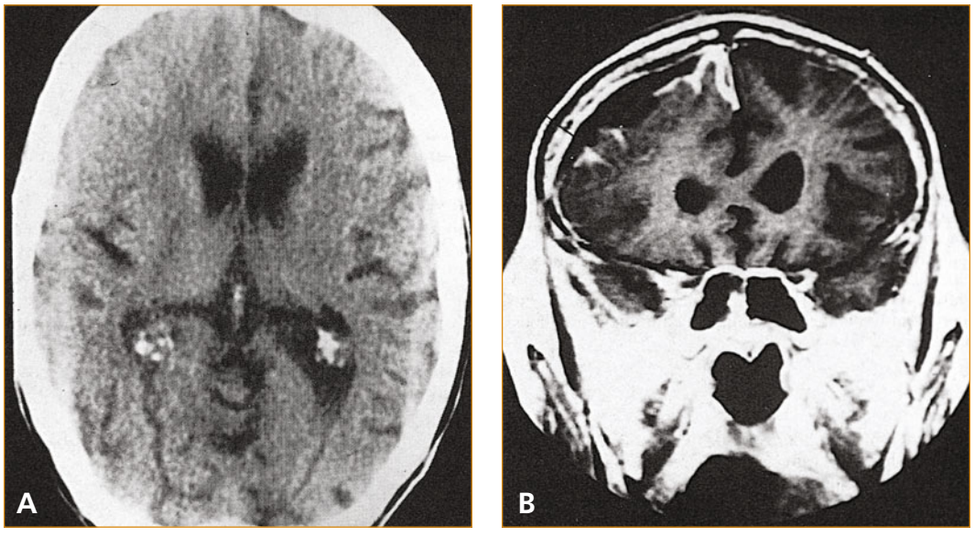


Figure 12-42. CT scan with contrast and MRI scan of subdural empyema done as part of a diagnostic work-up. **A**, CT scan reveals effaced sulci over the right hemisphere, with only minimal mass effect. **B**, However, MRI scanning with contrast reveals the large subdural empyema with mass effect.

CT with contrast and MRI scans are the diagnostic studies of choice for subdural empyema. Routine blood tests may reveal an elevated leukocyte count, especially in acute subdural empyema. Lumbar puncture is usually contraindicated because of focal deficits, increased intracranial pressure, and abnormalities on CT or MRI scans. When lumbar puncture is performed, the picture is one of parameningeal inflammatory response with an increased cell count; about 15% of cases have more than 1000 cells per mm^3. The response is acute with greater than 50% polymorphonuclear leukocytes in about 70% of cases. The glucose level is usually normal and cultures are usually negative (in greater than 90% of cases). The differential diagnosis includes epidural abscess, brain abscess, intracerebral thrombophlebitis, subdural hematoma, meningoencephalitis, pyogenic meningitis (especially after infarction has occurred), herpes simplex encephalitis, cysticercosis, and cerebral neoplasm.

Treatment consists of the immediate deployment of parenteral antibiotics, followed by surgical drainage. Empirical antibiotic therapy could include a third-generation cephalosporin (*eg*, ceftriaxone) for blood spectrum coverage, plus metronidazole for anaerobes and vancomycin for methicillin-resistant staphylococci. Mortality remains high around 20%. Prognosis is dependent on the level of consciousness at the time of treatment. (*From* Greenlee [25]; with permission.)

Clinical Manifestations of Brain Abscess

Manifestation	Percent (approximations)
Headache	75
Fever	50
Nausea/vomiting	50
Focal neurologic deficits	50
Altered mental status	50
Seizures	30
Signs of systemic infection	30
Nuchal rigidity	25
Papilledema	25

Figure 12-43. Clinical manifestations of brain abscess. The clinical manifestations of brain abscess depend upon the location of the lesion, whether the lesion is single (75% of cases) or multiple, and the duration of the process (fulminant or indolent, hours to several months—average 10 to 13 days). In most cases, the manifestations are those of an expanding intracerebral mass with few signs of infection. The headache may be focal, from a mass lesion, or diffuse, suggesting increased intracranial pressure. Focal neurologic deficits and seizures are usually caused by the mass itself, while nausea or vomiting, papilledema, and altered mental status are due to increased intracranial pressure. Focal deficits include hemiparesis, hemianopsia, hemisensory loss, and aphasia. About 25% of abscesses involve the posterior fossa, primarily the cerebellum.

Brain Abscess: Predisposing Conditions, Site of Abscess, and Microbiology

Predisposing Conditions	Site of Abscess	Usual Isolate(s) from Abscess
Contiguous site of primary infection		
Otitis media and mastoiditis	Temporal lobe or cerebellar hemisphere	Streptococci (anaerobic or aerobic), *Bacteroides fragilis*, Enterobacteriaceae
Frontoethmoidal sinusitis	Frontal lobe	Predominantly streptococci, *Bacteroides*, Enterobacteriaceae, *Staphylococcus aureus*, and *Haemophilus* species
Sphenoidal sinusitis	Frontal or temporal lobe	Same as in frontoethmoidal sinusitis
Dental sepsis	Frontal lobe	Mixed *Fusobacterium, Bacteroides*, and *Streptococcus* species
Penetrating cranial trauma or postsurgical infection	Related to wound	*S. aureus*, streptococci, Enterobacteriaceae, *Clostridium* species
Distant site of primary infection		
Congenital heart disease	Multiple abscess cavities; middle cerebral artery distribution common but may occur at any site	Viridans, anaerobic, and microaerophilic streptococci; *Haemophilus* species
Lung abscess, empyema, bronchiectases	Same as in congenital heart disease	*Fusobacterium, Actinomyces, Bacteroides*, streptococci, *Nocardia asteroides*
Bacterial endocarditis	Same as in congenital heart disease	*S. aureus*, streptococci
Compromised host (immunosuppressive therapy, malignancy, or AIDS)	Same as in congenital heart disease	*Toxoplasma*, fungi, Enterobacteriaceae, *Nocardia, L. monocytogenes*, *Mycobacterium* species

Figure 12-44. Predisposing conditions, site of abscess, and microbiology in brain abscess. Brain abscesses are usually associated with a contiguous site of infection, head trauma or surgery, and hematogenous spread from distant sites of infection. A contiguous site of infection usually accounts for about 40% to 50% of the cases; hematogenous spread, for about 25% to 35%; head trauma or surgery, for about 10%; and there is no obvious predisposing factor in about 15%. Unlike other age groups, brain abscess complicates meningitis in neonates. The predisposing condition plays a definite role regarding the site of the abscess in the brain and which organisms cause the abscess. (*Adapted from* Wispelwey *et al*. [26].)

A Microbiologic Etiology of Brain Abscess in the Immunologically Uncompromised Host

Etiologic Organisms	Isolation Frequency, %
Staphylococcus aureus	10–15
Enterobacteriaceae	23–33
Streptococcus pneumoniae	< 1
Haemophilus influenzae	< 1
Streptococci (*S. intermedius* group, including *S. anginosus*)	60–70
Bacteroides and *Prevotella* species	20–40
Fungi	10–15
Protozoa, helminths*	

**Heavily dependent on geographic locale.*

B Microbiologic Etiology of Brain Abscess in the Immunologically Compromised Host

Abnormal Cell-mediated Immunity	Neutropenia or Neutrophil Defects
Toxoplasma gondii	Aerobic gram-negative bacteria
Nocardia asteroides	*Aspergillus* species
Cryptococcus neoformans	*Zygomycetes*
Listeria monocytogenes	*Candida* species
Mycobacterium species	

Figure 12-45. Microbiologic etiology of brain abscess in the immunologically uncompromised host (**A**). In the preantibiotic era, *Staphylococcus aureus*, streptococci, and coliform bacteria were the common isolates from brain abscess. In the past 20 years, however, anaerobes (streptococci intermedius group, *Bacteroides* species) are probably the most common cause. Microbiologic etiology of brain abscess in the immunologically compromised host (**B**). Patients with AIDS, underlying malignancy, or those treated with immunosuppressive agents are at an increased risk for developing brain abscess. Fungi and parasites are also important diagnostic considerations in these patients. Neutropenia and neutrophilic defects are most often due to chemotherapy. (**A**, *adapted from* Wispelwey and Scheld [27]; **B**, *adapted from* Wispelwey *et al*. [26].)

A Differential Diagnosis of Brain Abscess in the Immunologically Uncompromised Host

- Subdural empyema
- Pyogenic meningitis
- Viral encephalitis (especially herpes simplex)
- Cysticercosis
- Cerebral infarction
- Mycotic aneurysms
- Epidural abscess
- Cerebral neoplasms
- Hemorrhagic leukoencephalitis
- Echinococcosis
- Cryptococcosis
- Central nervous system vasculitis
- Chronic subdural hematoma
- Intracerebral thrombophlebitis

B Differential Diagnosis of Brain Abscesses in Patients With AIDS

- Toxoplasmosis
- Primary central nervous system lymphoma
- *Mycobacterium tuberculosis*
- *Mycobacterium avium-intracellulare*
- Progressive multifocal leukoencephalopathy
- *Cryptococcus neoformans*
- *Candida* species
- *Listeria monocytogenes*
- *Nocardia asteroides*
- *Salmonella* group B
- *Aspergillus* species

Figure 12-46. Differential diagnosis of brain abscess. **A**, The differential diagnosis in the immunologically uncompromised host includes entities causing focal neurologic deficits, which are usually seen early in the course, and diffuse manifestations, which are seen later in the course of brain abscess. **B**, In AIDS patients, focal neurologic infections and processes of diverse and unusual etiologies have been recognized. The most common cause of focal neurologic lesions is toxoplasmosis, followed by lymphoma. (**A**, *adapted from* Wispelwey [28]; **B**, *adapted from* Wispelwey *et al*. [26].)

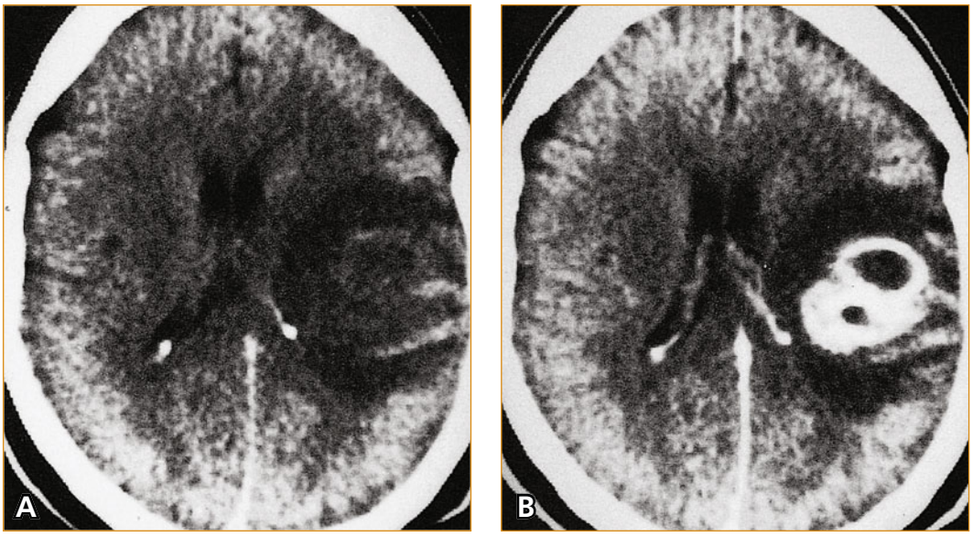


Figure 12-47. CT imaging studies for brain abscess. Routine laboratory studies are usually not helpful; they may show peripheral leukocytosis and increased erythrocyte sedimentation rate, but these findings are nonspecific. In addition to complete blood count, chest radiograph, electrocardiogram, and echocardiogram as needed, blood cultures should also be obtained. Lumbar puncture may reveal a parameningeal response, but the procedure is usually contraindicated until an imaging study of the brain has been performed. CT plain imaging and with contrast should be performed. MRI is even more sensitive, and reveals abscess or cerebritis at earlier stages of development than CT. **A**, Plain axial CT reveals mass effect in the left hemisphere with effacement of the sylvian fissure and the ipsilateral ventricle. **B**, With contrast, CT reveals a multiloculated ring enhanced lesion. The surrounding area of decreased attenuation represents cerebral edema. (**A**, *from* Wispelwey *et al*. [26]; with permission; **B**, *from* Falcone and Post [29]; with permission.)

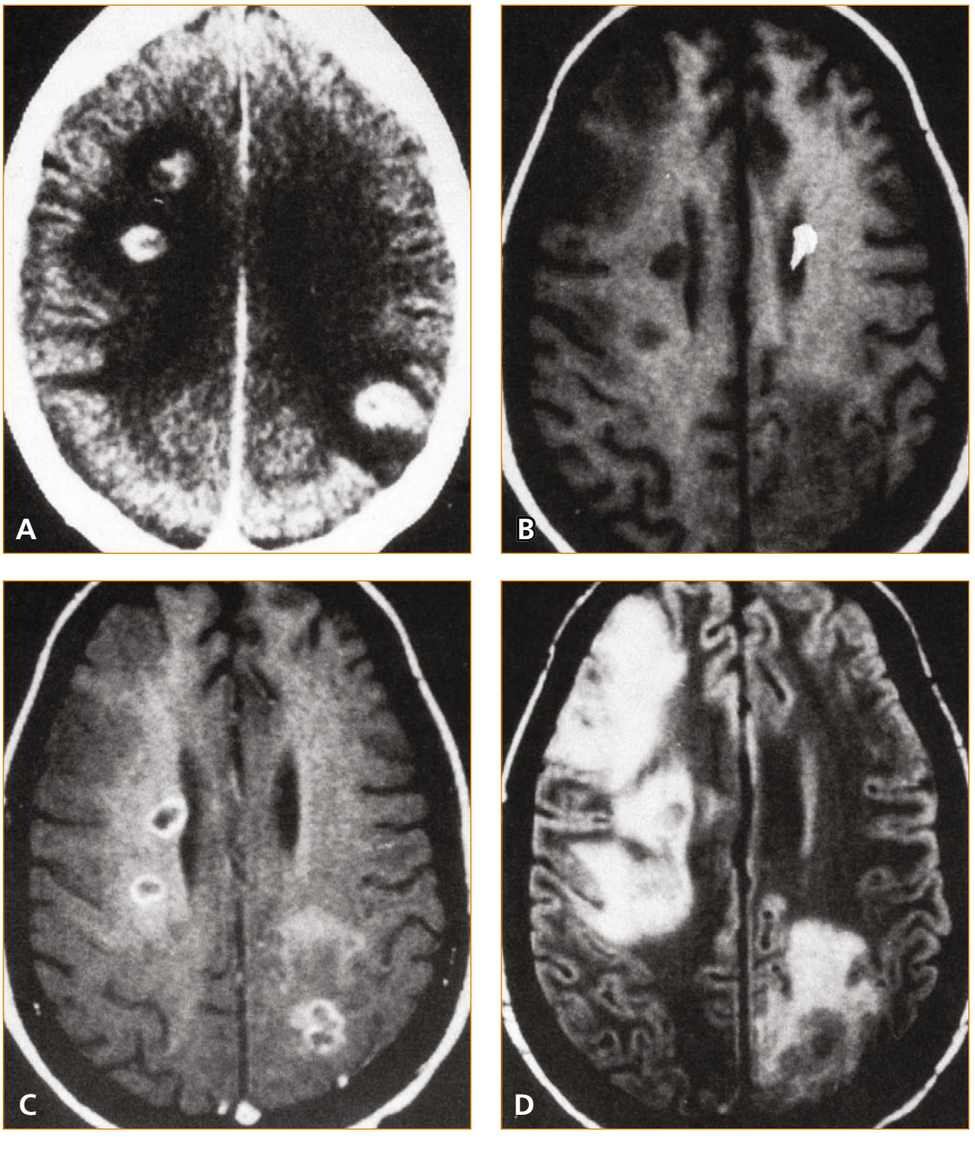


Figure 12-48. **A**, Axial CT scan showing multiple areas of contrast enhancement in a patient with AIDS and cerebral toxoplasmosis. **B**, T1-weighted images showing periventricular and gray–white junction lesions consistent with hematogenous dissemination. **C**, After gadolinium administration, contrast enhancement is seen on the T1-weighted image corresponding to that in **B**. **D**, Axial T2-weighted image showing edema surrounding multiple cortical and subcortical lesions. (*From* Kastenbauer *et al*. [30], with permission.)

Treatment of Brain Abscess

- Surgical treatment
  - Aspiration
  - Excision—when aspiration fails
- Medical treatment
  - Antimicrobal therapy—empirical
    - Community acquired, immunocompetent patient
      - Third-generation cephalosporin and metronidazole
    - Posttraumatic or postoperative
      - Third-generation cephalosporin and vancomycin
  - Corticosteroids—only for severe edema with mass effect and possible herniation
  - Anticonvulsant (AC) for seizures
    - Start AC for patients having seizures
    - Prophylactic AC controversial
  - Ventricular drainage for hydrocephalus

Figure 12-49. Treatment of brain abscess. Treatment of brain abscess usually consists of both surgical and medical therapy. Surgical treatment is generally contraindicated when there are multiple abscesses. Multiloculated abscesses are excised at times. Medical therapy consists of empirical antibiotic therapy until specific agents and sensitivities are determined—corticosteroids for life-threatening mass effects, anticonvulsants for seizures, and ventricular drainage for hydrocephalus.

Viral Infections

Viral Infections of the Nervous System

RNA Viruses	Representative Viruses Responsible for Neurologic Disease
Enterovirus (EV) (picornavirus)	Poliovirus
	Coxsackievirus
	Echovirus
	Enterovirus 70 and 71
Hepatovirus (picornavirus)	Hepatitis A
Togavirus: alphavirus (arbovirus)	Equine encephalitis (Eastern, Western, Venezuela)
Flavivirus (arbovirus)	St. Louis encephalitis
	West Nile encephalitis
	Japanese encephalitis
	Tick-borne encephalitis
Bunyavirus (arbovirus)	California encephalitis
Reovirus: coltivirus (arbovirus)	Colorado tick fever
Togavirus:rubivirus	Rubella
Orthomyxovirus	Influenza
Paramyxovirus	Measles and subacute sclerosing panencephalitis
	Mumps
Arenavirus	Lymphocytic choriomeningitis
Rhabdovirus	Rabies
Retrovirus	HIV, AIDS
	Human T-cell lymphotropic virus (HTLV)
DNA Viruses	
Herpesviruses	Herpes simplex (HSV)
	Varicella-zoster (VZV)
	Cytomegalovirus (CMV)
	Epstein-Barr (EBV) (infectious mononucleosis)
	Human herpes virus (6–8)
Papovavirus	Progressive multifocal leukoencephalopathy (PML)
Poxvirus	Vaccinia
Adenovirus	Adenovirus serotypes

Figure 12-50. Viral infections of the nervous system. The numerous viruses causing nervous system infections can be classified according to virus characteristics and the type of disease produced. Viruses are classified according to their nucleic acid type (RNA or DNA), sensitivity to lipid solvents (enveloped vs nonenveloped), and by their size. The infections produced may be either acute or chronic. In temperate zones of the northern hemisphere some of the viruses causing meningitis and encephalitis have a distinct seasonal activity. This is especially true for the enteroviruses and the mosquito-borne and tick-borne arboviruses that have peak epidemic activity in the spring and summer. Mumps is more often seen in late winter or spring and lymphocytic choriomeningitis in the fall and winter. Herpes viruses are endemic and cause disease in any season. (*Adapted from* Jubelt [31].)

Figure 12-51. Acute viral syndromes of the central nervous system (CNS). Acute viral infections of the CNS may cause three syndromes: viral (aseptic) meningitis, encephalitis, and myelitis. Acute viral meningitis is a self-limited illness, accompanied by fever, headache, photophobia, and nuchal rigidity. Encephalitis implies involvement of the brain parenchyma, causing alteration of consciousness, seizures, and focal neurologic deficits. When both meningeal and encephalitic signs are present on examination, the term *meningoencephalitis* is sometimes used in the diagnosis. Viral myelitis is an infection of the spinal cord. The myelitis is most often considered a demyelinating white matter syndrome (transverse myelitis), but spinal motor neurons (poliomyelitis, paralytic disease), sensory neurons, and autonomic neurons (bladder paralysis) may be affected. If encephalitis and myelitis occur together, the term *encephalomyelitis* is used. The cerebrospinal fluid formula in all these viral syndromes is similar, usually showing a mononuclear pleocytosis of 50 to 500 cells per mm^3, normal glucose level, and elevated protein level and pressure. A clinical continuum exists between viral meningitis and encephalitis, as the same spectrum of viruses cause both syndromes, although some viruses more often cause meningitis and others, encephalitis. The role of mumps virus in the etiology of these syndromes has decreased greatly since the 1970s because of vaccination programs. (*Adapted from* Centers for Disease Control and Prevention [32].)

Relative Frequency of Meningitis and Encephalitis of Known Viral Etiology

Viral Agent	Viral Meningitis, 1976*, Patients, *n (%)*	Viral Encephalitis, 1976†‡, Patients, *n (%)*	Viral Encephalitis, 1981‡§, Patients, *n (%)*
Enteroviruses	324 (83)	13 (2)	82 (23)
Mumps	28 (7)	71 (10)	7 (2)
Arboviruses	6 (2)	424 (60)	107 (30)
Herpes simplex	15 (4)	69 (10)	97 (27)
Measles	3 (1)	44 (6)	1 (0.3)
Varicella	5 (1)	58 (8)	30 (8)

**Data from Centers for Disease Control and Prevention: Aseptic Meningitis Surveillance, Annual Summary from 1976. Issued January 1979. There were 2534 cases of indeterminate etiology.*
†Data from Centers for Disease Control and Prevention: MMWR–Annual Summary 1977. There were 1121 cases of indeterminate etiology.
‡Includes both primary and postinfectious encephalitis. Almost all cases caused by measles and varicella are postinfectious.
§There were 1121 cases of indeterminate etiology.

Virologic and Serologic Studies for Acute CNS Viral Syndromes

Agent	Specimens for Virus Detection	Serologic Studies
Enteroviruses		
Polio	Throat washing, stool, and CSF	Acute/convalescent sera
Coxsackie	Throat washing, stool, and CSF	
Echovirus	Throat washing, stool, and CSF	
Lymphocytic choriomeningitis virus	Blood, CSF	Acute/convalescent sera
Mumps	Saliva, throat washing, CSF, urine	Acute/convalescent sera
Measles	Throat washing, urine, conjuctival secretions	Acute/convalescent sera
		IgM ELISA of serum
Arboviruses	Blood, CSF	IgM antibody ELISA of CSF or serum
		Acute/convalescent sera
Herpesviruses		
HSV		
Type 1	Brain biopsy, PCR of CSF	CSF antibody detection after day 10
		Acute/convalescent sera (±)
Type 2	CSF, genital and vesicle fluid, blood	Acute/convalescent sera
Varicella-zoster	Vesicle fluid, CSF	Acute/convalescent sera
Cytomegalovirus	Urine, saliva, blood (circulating leukocytes), CSF	Acute/convalescent sera
Epstein-Barr virus	Rarely cultured	Acute sera for antibody profile
Rabies	Saliva, CSF, neck skin biopsy, brain biopsy	Serum after day 15
Adenovirus	Nasal or conjunctival swab, urine, stool	Acute/convalescent sera
Influenza	Throat washing	Acute/convalescent sera

Figure 12-52. Specific virologic (culture, nucleic acid detection, antigen detection) and serologic studies for the diagnosis of acute central nervous system (CNS) viral syndromes. Viruses may be isolated from extraneural sites. For most infections, except reactivated infections such as with herpes simplex virus type 1 or herpes zoster, extraneural isolation is usually diagnostic. Obviously if virus can be isolated from the cerebrospinal fluid (CSF), that is preferred. Detection of virus-specific nucleic acid by polymerase chain reaction (PCR) is now readily available for most viral infections [33].

Continued on the next page

Figure 12-52. *(Continued)* Antigen detection usually requires the use of biopsy material. Serologic studies require a fourfold increase between the acute and convalescent specimen to be considered positive. Acute phase sera should be obtained immediately or as soon as infection is suspected. If the acute phase sera is not obtained until the end of the first week of the disease, the chances of seeing a fourfold rise drops to 50%. Most viral infections of the CNS result in the intrathecal synthesis of specific antibody. When analyzing CSF antibody synthesis one looks for an increased CSF to serum antibody ratio. Therefore, paired CSF and serum samples are required. A correction should also be used for blood-brain barrier breakdown, which results in serum to CSF antibody leakage. This can be done by using CSF to serum albumin or other viral antibody ratios. Unfortunately, most antibody studies are not positive until at least 1 week after the onset of infection. ELISA—enzyme-linked immunosorbent assay. (*Adapted from* Jubelt [34].)

Viral Meningitis

Figure 12-53. Clinical manifestations of acute viral meningitis. Acute viral meningitis is sometimes referred to as "aseptic" meningitis, but the terms are not synonymous, because agents other than viruses also cause aseptic meningitis, for example, parameningeal infection, autoimmune disease, vasculitis, and chemicals. Acute viral meningitis usually begins abruptly with a combination of central nervous system signs of nuchal rigidity, headache, photophobia, and occasionally lethargy along with systemic manifestations. If the alteration in the level of consciousness is more pronounced than lethargy, another diagnosis should be considered. The cerebrospinal fluid (CSF) profile is that of all viral syndromes, with lymphocytic pleocytosis, mildly elevated protein levels, and a normal glucose level. Because the intensity of the inflammatory response in the CSF is low (usually 0 to 500 cells per mm^3), nuchal rigidity is usually the only sign of meningeal irritation, and Kernig's and Brudzinski's signs are often absent. In a few cases, however, marked pleocytosis may be seen (greater than 1000 cells per mm^3), often accompanied by Kernig's and Brudzinski's signs. The meningitis is self-limited, resolving usually in 1 week. URI—upper respiratory infection.

Clinical Manifestations of Acute Viral Meningitis

Systemic Manifestations	Central Nervous System Manifestations
Fever	Headache, usually frontal or retro-orbital
Malaise	Nuchal rigidity
Anorexia	Photophobia
Myalgia	Lethargy
Nausea and vomiting	
Agent-specific pharyngitis, URI, abdominal pain, diarrhea	

Figure 12-54. Differential diagnosis of acute viral meningitis. It is important to exclude nonviral causes of meningitis that may require specific therapy or more emergent therapy. During the first 24 hours of viral meningitis polymorphonuclear leukocytes may appear in the cerebrospinal fluid sample, similar to bacterial meningitis. In partially treated bacterial meningitis, the glucose level may be normal. Usually in tuberculous, fungal, spirochetal, and parasitic meningitis, the glucose level is depressed. Cytologic examination should differentiate neoplastic meningitis, whereas serologic studies help exclude autoimmune disease. Imaging studies usually detect parameningeal inflammation.

Differential Diagnosis of Acute Viral Meningitis

- Bacterial meningitis
  - Early (0–24 h)
  - Also listeriosis, mycoplasmosis, brucellosis
- Tuberculous meningitis
- Fungal meningitis
- Spirochetal meningitis: syphilis, Lyme disease, leptospirosis
- Parasitic meningitis
- Parameningeal infections
- Neoplastic meningitis
- Autoimmune and inflammatory diseases; lupus, sarcoid, vasculitis
- Drug reactions: nonsteroidal anti-inflammatory agents, sulfamethoxazole, trimethoprim, trimethoprim-sulfamethoxazole, isoniazid, carbamazepine, azathioprine, intravenous immune globulin, intravenous monoclonal OKT3
- Chemical meningitis: intrathecal drugs, central nervous system tumors, myelography, isotope cisternography

Figure 12-55. Neurologic syndromes associated with enteroviruses. Enteroviruses are the most common cause of viral meningitis. In addition to aseptic meningitis, several other syndromes have been associated with enteroviruses. Encephalitis is the second most common syndrome caused by enteroviruses, and in some years, enteroviruses account for a fourth of all cases of encephalitis of known etiology. The encephalitis is usually mild, with obtundation, coma (rarely), isolated seizures, behavior changes, and mild focal defects (rarely severe). The prognosis is excellent with resolution in 3 to 4 weeks, although concentration and intellectual abilities may not resolve for 3 to 6 months. The exceptions to this good prognosis are the fulminant encephalitis cases seen with group B coxsackievirus systemic neonatal infections, the chronic encephalitis that appears with chronic persistent infection in agammaglobulinemic patients, and the EV71 brain stem encephalitis case seen in Asian-Pacific regions. Paralytic disease is discussed in the section on myelitis and related infections (*see* Figs. 12-77–12-79). Acute cerebellar ataxia and isolated cranial nerve palsies are infrequent and have a good prognosis. Chronic (persistent) enterovirus infections are caused mainly by echoviruses and live vaccine strains of polioviruses in agammaglobulinemic children. The echoviruses cause chronic encephalitis that progresses over several years, possibly accompanied by dermatomyositis. Polioviruses cause chronic encephalitis, but because of ensuing paralysis the course usually lasts only months to a year. The prognosis is poor despite the intrathecal administration of specific antibody, which may result in temporary remissions but usually not clearance of virus from the central nervous system. Systemic manifestations of enterovirus infection include hand-foot-and-mouth disease, other rashes, upper respiratory infections, pleurodynia, and pericarditis. (*Adapted from* Jubelt and Lipton [35].)

Neurologic Syndromes Associated with Enteroviruses

Syndrome	Virus Type
Aseptic meningitis	Polioviruses 1–3
	Coxsackieviruses A1–11, 14, 16–18, 22, 24
	Coxsackieviruses B1–6
	Echoviruses 1–7, 9, 11–25, 27, 30–33
Encephalitis	Enterovirus 71
	Polioviruses 1–3
	Coxsackieviruses A2, 4–9
	Coxsackieviruses B1–6
	Echoviruses 2–4, 6, 7, 9, 11, 14, 17–19, 25
	Enterovirus 71
	Enterovirus 72 (hepatitis A virus)
Paralytic disease	Poliovirus 1–3
	Coxsackieviruses A2–4, 6–11, 14, 16, 21
	Coxsackieviruses B1–6
	Echoviruses 1–4, 6, 7, 9, 11, 13, 14, 16, 18–20, 30, 31
	Enteroviruses 70, 71
Acute cerebellar ataxia	Polioviruses 1, 3
	Coxsackieviruses A2, 4, 7, 9, B1–6
	Echoviruses 6, 9
	Enterovirus 71
Isolated cranial nerve palsies, especially facial	Poliovirus 1–3
	Coxsackieviruses A10, B5
	Echoviruses 4
	Enteroviruses 70
Chronic infections	Polioviruses 1–3 (vaccine-like strains)
	Coxsackieviruses A15, B3
	Echoviruses 2, 3, 5, 7, 9, 11, 15, 17–19, 22, 24, 25, 27, 29, 30, 33

Herpes Simplex Virus Type 2

Pathogenesis of Herpes Simplex Type 2 Infections

	Adolescents and Adults	Newborns	Immunocompromised Host
Transmission	Venereal	In utero or at delivery	Venereal
Primary infection	Genital herpes; aseptic meningitis	Disseminated infection with hepatic and adrenal necrosis and encephalitis	Genital herpes
			Cutaneous herpes
			Disseminated infection with encephalitis
Latency	Sacral dorsal root ganglia	Unknown, usually fatal	Same as adolescent and adults
Recurrence	Genital herpes	—	Same as adolescent and adults if patient survives
	Cutaneous herpes		
	Aseptic meningitis		
	Radiculitis		

Figure 12-56. Pathogenesis of herpes simplex type 2 (HSV-2) meningitis. HSV-2 is spread primarily by venereal contact. Most primary infections occur between the ages of 14 and 35 years, and most often manifest as genital infections of the penis in men and of the vulva, perineum, buttocks, cervix, and vagina in women. Approximately 25% of those infected by venereal transmission develop aseptic meningitis as part of the primary infection.

Continued on the next page

Figure 12-56. *(Continued)* Primary infection of a fetus can occur in utero or during delivery through an infected birth canal, which may result in severe and often fatal disseminated infection with encephalitis of the neonate. A similar disseminated infection may occur in the immunocompromised host after venereal transmission. Because the sacral ganglia receive sensory fibers from the external genitalia, the virus is transported axonally to the ganglia, where it becomes latent; the virus later reactivates and causes recurrent disease. Recurrent disease usually is limited to the genitalia, but aseptic meningitis and radiculitis may occur. Recurrent meningitis is sometimes referred to as Mollaret's meningitis. Radiculitis is manifested by dysesthesia, which is often painful, may be burning or lancinating in character, and may cause sciatica. Sacral radiculitis may also result in bladder and bowel dysfunction, such as retention or incontinence.

Figure 12-57. Treatment of herpes simplex type 2 infections. Acyclovir is the major drug in use today for treating herpes simplex infections. It is available in three formulations: intravenous (IV), oral, and topical (5% ointment). For the primary genital infection, oral acyclovir is indicated. Treatment for aseptic meningitis has not been studied, but it is a self-limited disease. Intravenous acyclovir is needed for disseminated infection with or without encephalitis. Frequent recurrences are usually treated in the immunocompetent host with 1 year of oral acyclovir for suppression. The immunocompromised host requires treatment for each recurrence and probably continuous oral treatment for suppression as a preventative measure.

Acyclovir Treatment of Herpes Simplex Type 2 Infections

Type of Infection	Recommended Treatment
Primary infection	
Genital lesions	Oral acyclovir, 200 mg daily 5× for 10 d
Aseptic meningitis	None or oral acyclovir (but not studied)
Disseminated infection with or without encephalitis	IV acyclovir, 10 mg/kg q8h for 21 d
Recurrent infection	
Immunocompetent host	
Infrequent	No treatment
Frequent	Oral acyclovir for suppression for up to 1 y, 200 mg tid or qid
Immunocompromised host	
Localized infection	Oral or IV acyclovir
Disseminated infection	IV acyclovir
Preventative	Oral acyclovir, 200 to 400 mg 2× to 5× per day

Viral Encephalitis

Figure 12-58. Clinical manifestations of acute viral encephalitis. The term encephalitis implies involvement of the brain parenchyma. Often the meningeal manifestations seen in acute viral meningitis are also present in addition to the signs of brain dysfunction (meningoencephalitis). The signs of brain dysfunction may be focal or diffuse; these may manifest as mental status changes, seizures (in greater than 50% of cases), or hard focal signs. All types of focal deficits have been reported. Viral encephalitis can be divided into primary and secondary types. In primary encephalitis, there is viral invasion and infection of the brain parenchyma, usually of the gray matter. Secondary encephalitis is postinfectious encephalitis (or encephalomyelitis) in which an immune-mediated attack against myelin and white matter apparently occurs. Despite the different locations (gray vs white matter) of these pathologic insults, one cannot distinguish between the two based on the clinical symptoms and signs. The cerebrospinal fluid profile is similar to that of any acute viral syndrome, with lymphocytic pleocytosis (usually 5 to 500 cells per mm^3), normal glucose levels, increased protein levels, and increased pressure.

Clinical Manifestations of Acute Viral Encephalitis

- Acute febrile illness of abrupt onset
- Systemic manifestations—malaise, anorexia, myalgias, pain, nausea and vomiting, diarrhea
- Meningeal irritation—headache, photophobia, nuchal rigidity
- Parenchymal (brain) dysfunction
  - Altered level of consciousness
    - Lethargy to coma
    - Confusion, disorientation
    - Delirium
  - Mental changes—personality and behavioral changes, including agitation, hallucinations, and psychosis
  - Seizures—focal or generalized
  - Extensor plantar responses and hyperreflexia
  - Focal deficits—less frequent
    - Aphasia
    - Ataxia
    - Hemiparesis
    - Tremor
    - Cranial nerve palsies

Differential Diagnosis of Acute Viral Encephalitis

Bacterial infections
- Parameningeal—epidural abscess, subdural empyema, brain abscess
- Tuberculous meningitis—late with parenchymal involvement
- Bacterial endocarditis
- Rocky Mountain spotted fever
- Brucellosis
- *Mycoplasma* pneumonia
- *Legionella* pneumonia

Fungal infections
- Fungal abscess
- Fungal meningitis—late with parenchymal involvement

Parasitic infections
- Toxoplasmosis
- Amebic meningoencephalitis
- Cysticercosis
- Malaria
- Trichinellosis
- Trypanosomiasis

Spirochete infections
- Lyme disease
- Leptospirosis

Noninfectious causes
- Encephalopathy—toxins, drugs, metabolic disorders
- Autoimmune and inflammatory causes—collagen vascular disease, vasculitis, sarcoid

Neoplasia
- Primary brain tumors
- Metastatic brain lesions

Figure 12-59. Differential diagnosis of acute viral encephalitis. A wide variety of diseases that affect the brain parenchyma can simulate acute viral encephalitis. The differential diagnosis includes both infectious and noninfectious diseases.

A Geographic Distribution of the Major Viral Encephalitides

Virus	Geographic Distribution
Japanese encephalitis	Eastern Asia, India
St. Louis encephalitis	US, Caribbean
California group encephalitis	North America
Eastern equine encephalitis	US Atlantic and Gulf coasts, Caribbean, South America
Western equine encephalitis	Western US and Canada, Central and South America
Venezuelan equine encephalitis	Texas, Florida, Central and South America
West Nile encephalitis	Africa, Middle East, eastern Europe, North America
Murray Valley encephalitis	Australia, New Guinea
Rocio	Brazil
Tick-borne encephalitis complex	Worldwide
Lymphocytic choriomeningitis	Americas, Europe, Africa
Mumps	Worldwide
Measles	Worldwide
Rabies	Worldwide (except UK and Japan)
Herpes simplex encephalitis	Worldwide
Epstein-Barr encephalitis	Worldwide
Varicella-zoster encephalitis	Worldwide
HIV	Worldwide

B Most Causes of Viral Encephalitides in the United States

Virus	Geographic Distribution
Herpes simplex	Nationwide
Mumps	Nationwide
St. Louis	Nationwide (esp. south and central)
California/La Crosse	Central and eastern US
Western equine	Western
Eastern equine	Atlantic and Gulf coasts
West Nile encephalitis	Nationwide
Colorado tick fever	Western US
Venezuelan equine	Texas and Florida
Rabies	Nationwide

Figure 12-60. Geographic distribution of major causes of encephalitides. The arboviruses (insect-borne) have distinct geographic locations throughout the world. Other viruses may occur in seasonal, epidemic, or endemic fashion depending on the geographic location. Therefore, the travel history may be very important for making the diagnosis. **A**, Major causes of viral encephalitides worldwide. **B**, Major causes of viral encephalitides in the United States. (*Adapted from* Hanley *et al*. [36] and Solomon [37].)

Clinical Manifestations of Herpes Simplex Encephalitis at Presentation

	NIAID Collaborative Study*	Swedish Study†
Symptoms		
Altered consciousness	97% (109/112)	100% (53/53)
Fever	90% (101/112)	100% (53/53)
Headache	81% (89/110)	74% (39/53)
Seizures	67% (73/109)	
Vomiting	46% (51/111)	38% (20/53)
Hemiparesis	33% (33/100)	
Memory loss	24% (14/59)	
Signs		
Fever	92% (101/110)	
Personality alteration (confusion, disorientation)	85% (69/81)	57% (30/53)
Dysphasia	76% (58/76)	36% (19/53)
Autonomic dysfunction	60% (53/88)	
Ataxia	40% (22/55)	
Hemiparesis	38% (41/107)	40% (21/33)
Seizures	38% (43/112)	62% (33/53)
Focal	(28/43)	
Generalized	(10/43)	
Both	(5/43)	
Cranial nerve deficits	32% (34/105)	
Papilledema	14% (16/111)	

**Data from Whitley et al. [38].*
†Data from Skoldenberg et al. [39].

Figure 12-61. Clinical manifestations of herpes simplex type 1 (HSV-1) encephalitis. HSV-1 causes a focal encephalitis involving the medial temporal and orbitofrontal lobes. However, at presentation, when the diagnosis needs to be made for institution of therapy, hard focal signs are present only in the minority of patients. The most common manifestations at presentation (alteration in consciousness and personality changes including bizarre behavior and hallucinations) are not very localizing and can be seen in diffuse processes. Localization of the lesion depends upon diagnostic tests. The numbers in parentheses are absolute numbers that represent the number of patients presenting with symptoms or signs divided by the total number of points for which they were asked or for which they looked. NIAID—National Institute of Allergy and Infectious Diseases.

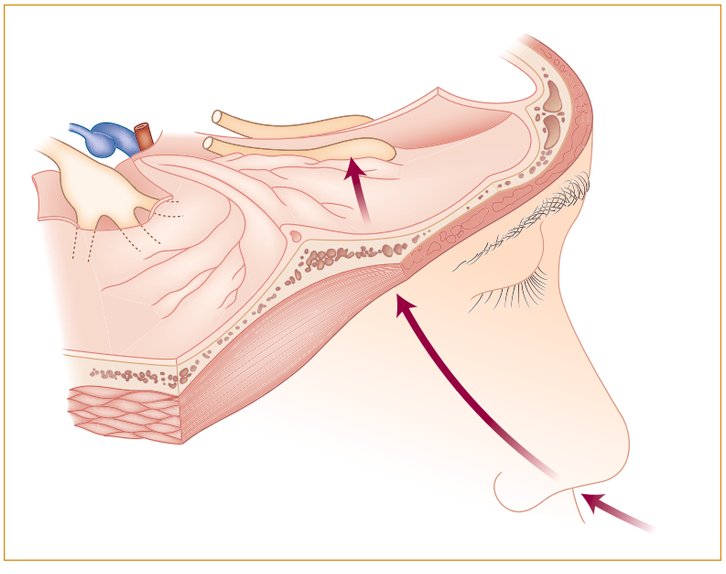


Figure 12-62. Pathogenesis of herpes simplex virus (HSV) encephalitis. Anatomical pathways may explain the localization of herpes simplex virus type 1 (HSV-1) encephalitis to the orbitofrontal and medial temporal lobes. Direct infections via the olfactory bulb could cause orbital-frontal infection with secondary spread to the temporal lobe. Recurrent sensory branches from the trigeminal ganglia project to the basilar dura of the anterior and middle cranial fossa. This may explain temporal lobe localization of HSV encephalitis when the virus reactivates in the trigeminal ganglia. Based on serologic studies, about 30% of HSV encephalitis is due to direct invasion and 70% from reactivation. (*Adapted from* Johnson [40].)

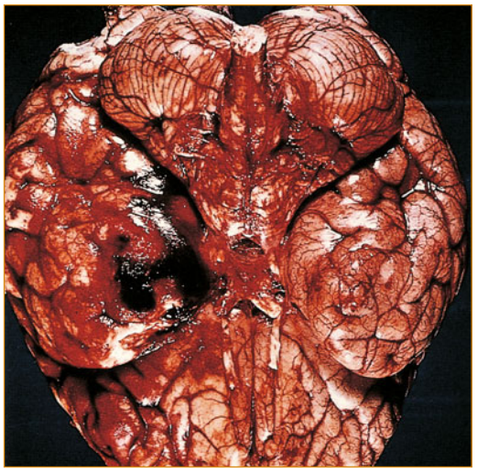


Figure 12-63. Gross anatomy of the brain in herpes simplex virus encephalitis. There is a hemorrhagic necrotic lesion of the left medial temporal lobe. As in this case, subarachnoid hemorrhage is frequent and results in the large number of erythrocytes often found in the cerebrospinal fluid. (*From* Hirano *et al*. [41]; with permission.)

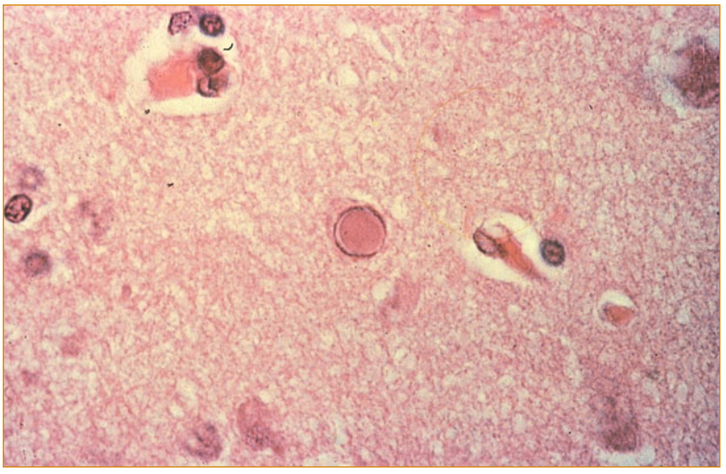


Figure 12-64. Histologic slide showing microscopic anatomy of herpes simplex virus (HSV) encephalitis (hematoxylin-eosin stain). Shown is a type A intranuclear inclusion body within the nucleus of a small nerve cell. These eosinophilic inclusion bodies may be seen in other herpes virus infections and subacute measles encephalitis. This section was taken from the temporal lobe cortex of a person with HSV encephalitis. The nuclear chromatin is marginated. These inclusion bodies can also be seen in glia and are a helpful diagnostic sign. (*From* Wilson [4]; with permission.)

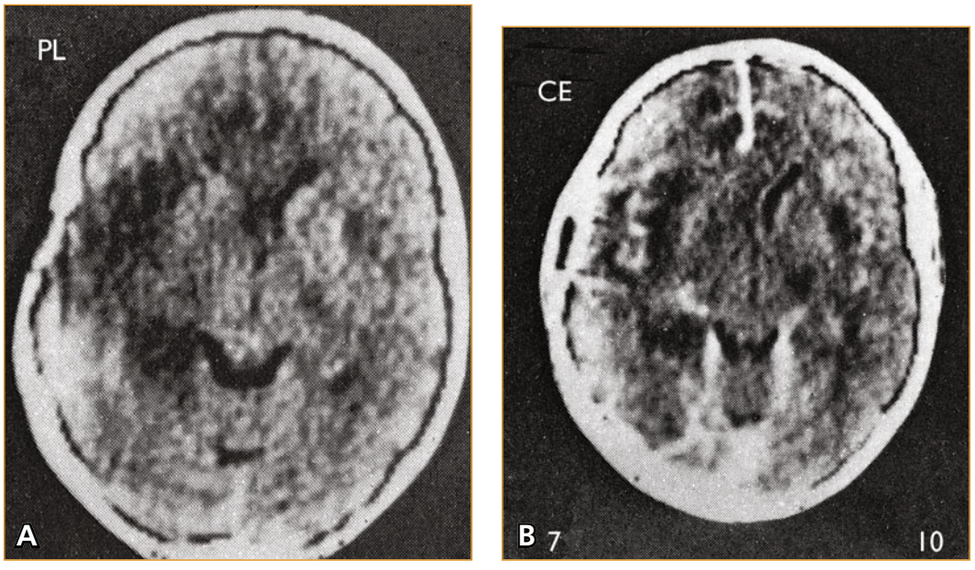


Figure 12-65. CT scans of herpes simplex virus (HSV) encephalitis. The initial diagnostic test should be a brain CT scan to exclude other lesions and to check for mass effect. Usually the CT scan does not become positive until the end of the first week of infection. If there is mass effect, treatment should commence with mannitol or steroids and acyclovir. Diagnosis can then be confirmed by MRI scanning. If the CT is normal or there is no mass effect, lumbar puncture should be performed. Within the first day or two of onset, 5% to 10% of cerebrospinal fluid (CSF) examinations are normal, but usually there is a lymphocytic pleocytosis, normal glucose, elevated protein, and pressure similar to other central nervous system viral infections. However, in HSV encephalitis there may be significant necrosis, hemorrhage, and erythrocytes in the CSF. The use of polymerase chain reaction for amplification of HSV DNA from the CSF is a rapid and sensitive method of diagnosis. If the CSF is abnormal, MRI scanning should be performed, and acyclovir should be started if the MRI is consistent with herpes encephalitis. If there is a delay in obtaining the MRI, then acyclovir should be started first. The electroencephalogram (EEG) can also be a useful test as it may reveal temporal lobe foci earlier than CT scanning. If the diagnosis is not confirmed from the MRI and EEG, then a brain biopsy may be needed. **A**, CT scan on day 10 revealing low-density lesion in the right temporal and deep frontal lobes. **B**, The corresponding enhanced CT scan reveals gyral enhancement in the sylvian fissure and insular regions, which are greater on the right. (*From* Davis *et al*. [42]; with permission.)

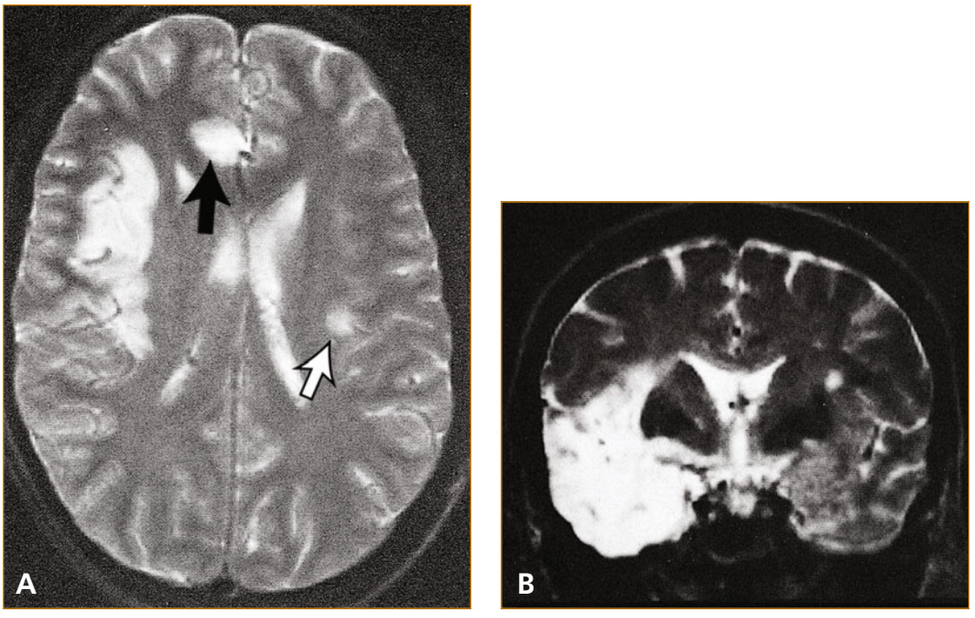


Figure 12-66. MRI scans used in the diagnosis of herpes simplex virus (HSV). MRI has become the diagnostic test of choice for HSV encephalitis and is abnormal in more than 90% of cases. MRI will usually reveal a hyperintense lesion with T2 weighting due to inflammation and edema within a day or two of onset, even when the CT scan is normal. Lesions may not only be seen in the temporal lobe but also in the orbital frontal lobes and insular cortex. **A**, T2-weighted axial MRI shows high signal intensity in the right insular cortex, medial right frontal cortex (*black arrow*), and left insular cortex (*white arrow*). **B**, T2-weighted coronal image shows increased signal in the left temporal lobe and beginning involvement of the right side. Coronal images are the most useful for seeing the lesion. (**A**, *from* Runge [43]; with permission; **B**, *from* Schroth *et al*. [44]; with permission.)

Arbovirus Encephalitis

Major Arboviral Encephalitides

Mosquito-borne Viruses	Location	Tick-borne Viruses	Location
Togaviridae (alphaviruses)		Flaviviridae (flaviruses)	
Eastern equine encephalitis	US Atlantic and Gulf coasts, Caribbean	Tick-borne complex	
		Far Eastern	Eastern Russia
Venezuelan equine encephalitis	Texas Florida, Central and South America	Central European	Eastern Europe, Scandinavia, France, Switzerland
Western equine encephalitis	Western US and Canada, Central and South America	Russian spring-summer	Eastern Europe, Asia
		Kyasanur Forest disease complex	India
Flaviviridae (flaviruses)			
St. Louis encephalitis	US, Caribbean	Negishi	Japan
Japanese encephalitis	Eastern Asia, India	Powassan	North central US, eastern Canada
Murray Valley encephalitis	Australia, New Guinea	Louping ill	Great Britain
Rocio	Brazil	Reoviridae (coltivirus)	
West Nile	Africa, Middle East, eastern Europe, North America	Colorado tick fever	US and Canadian Rocky Mountains
Ilheus	Central and South America		
Bunyaviridae (bunyaviruses)			
California encephalitis group			
California	Western US		
La Crosse	Central and eastern US		
Tahyna (phlebovirus)	Central and southern Europe		
Rift Valley fever	East and South Africa		

Figure 12-67. Major arboviral encephalitides in the world. The term *arbovirus* is no longer used as official viral nomenclature. However, it is still useful to designate all the anthropod-borne viruses. There are about 20 arboviruses worldwide that primarily cause encephalitis. Many other arboviruses cause systemic febrile illnesses or hemorrhagic fevers (*eg*, yellow fever virus) but only infrequently, encephalitis. Arboviruses are usually geographically localized and seasonally restricted. (*Adapted from* Hanley *et al*. [36] and Solomon [37].)

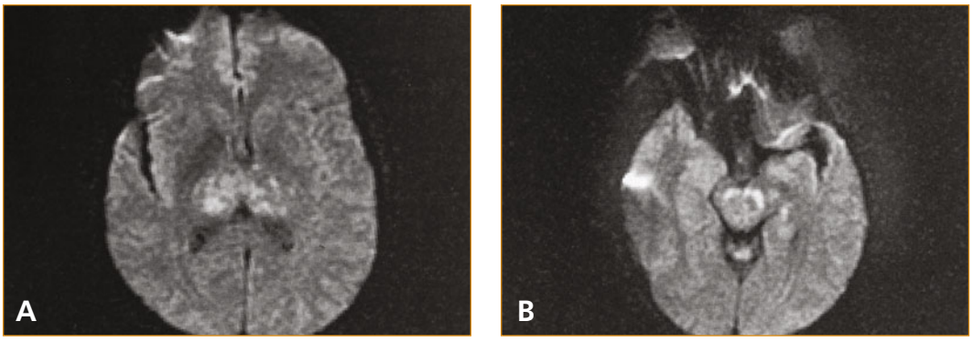


Figure 12-68. West Nile virus neuroinvasive disease. West Nile virus (WNV) infections appeared in New York City in August 1999. Since then, the virus has spread to all of the continental United States, Canada, and Mexico. WNV is now the most common cause of epidemic viral encephalitis in the United States with nearly 20,000 confirmed cases. Symptomatic infections include generalized illness (West Nile fever) and West Nile neuroinvasive disease (WNND), which includes meningitis, encephalitis, brainstem encephalitis, and poliomyelitis-like acute flaccid paralysis. On cerebrospinal fluid (CSF) analysis, about 40% of patients with WNND have a neutrophil predominance in the initial CSF examination. Diagnosis depends primarily on finding specific IgM antibodies in the CSF. Neuroimaging studies may help with diagnosis. MRI abnormalities have been reported in 20% to 70% of cases and appear to increase over the first week of illness. Abnormalities are usually seen in deep gray matter structures (basal ganglia, thalami), brainstem, and cerebellum on T2, FLAIR, and diffusion-weighted images (DWI). MRI DWI images on day 6 of WNV encephalitis in thalami (**A**) and substantive nigra (**B**). There is no specific treatment at the present time. (*From* Davis *et al*. [45]; with permission.)

Rabies

Clinical Manifestations of Rabies

Finding	%
Fever	73
Dysphagia	58
Altered mental state	55
Pain, paresthesia referable to site of exposure	45
Excitement, agitation	45
Paralysis, weakness	26
Hydrophobia	21
Hypersalivation	16
Nausea, vomiting	18.6
Malaise	16.3
Dyspnea	14
Headache	14
Convulsions, spasma	9.1
Coma	4.5
Miscellaneous (lethargy, dysuria, anorexia, hydrophobia)	16.3
No history of rabies exposure	16

Figure 12-69. Clinical manifestations of rabies, frequency during the course of the disease. At onset, about half of the patients have pain or paresthesia at the bite site. Other initial manifestations include fever, malaise, anorexia, and drowsiness. (*Adapted from* Robinson [46].)

Clinical Progression of Rabies

Stage	Duration	Clinical Manifestations
Incubation period	30–90 d: ~ 50% of cases < 30 d: ~ 25% > 90 d to 1 y: ~ 5% > 1 y: ~ 5%	No clinical findings
Prodrome and early clinical symptoms	2–10 d	Paresthesia and/or pain at site of bite Fever, malaise Anorexia, nausea, vomiting Headache
Acute neurologic disease	2–7 d	"Furious rabies" (80% of cases) Hallucinations, bizarre behavior, anxiety, agitation, biting Autonomic dysfunction "Paralytic rabies" (20% of cases) Flaccid paralysis Paresis and plegias Ascending paralysis
Coma	0–14 d	SIADH Diabetes insipidus Multiorgan failure Respiratory or cardiac failure
Death (common)	Variable	—
Recovery (rare)	Variable	Several sequelae

Figure 12-70. Clinical progression of rabies. The clinical course of rabies consists of five stages. The prolonged incubation period lasts more than 90 days in 25% and more than 1 year in 5% of cases. After the initial manifestations with lethargy, a state of excitability ensues, when external stimuli may cause focal or generalized convulsions. Spasmodic contractions of the larynx and pharynx are precipitated by any attempt to drink or eat, thus the term *hydrophobia*. During this stage the temperature may reach 105° to 107° F. This hyperexcitability stage passes into the comatose stage, with generalized paralysis. Occasionally, the disease begins as "dumb rabies," in which flaccid paralysis of one or more limbs occurs rather than a hyperexcitable period. Death is usually caused by respiratory paralysis followed by cardiovascular collapse. SIADH—syndrome of inappropriate secretion of antidiuretic hormone. (*Adapted from* Rupprecht and Hemachudha [47].)

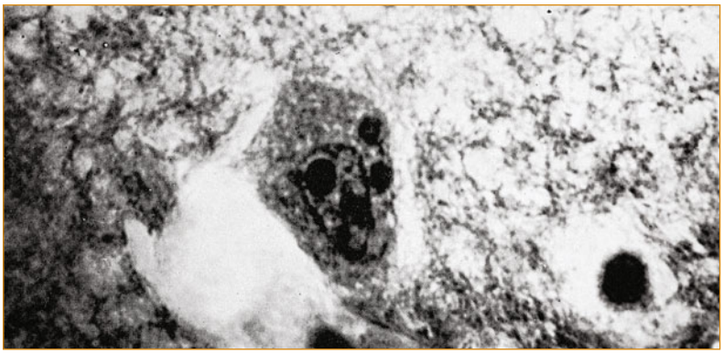
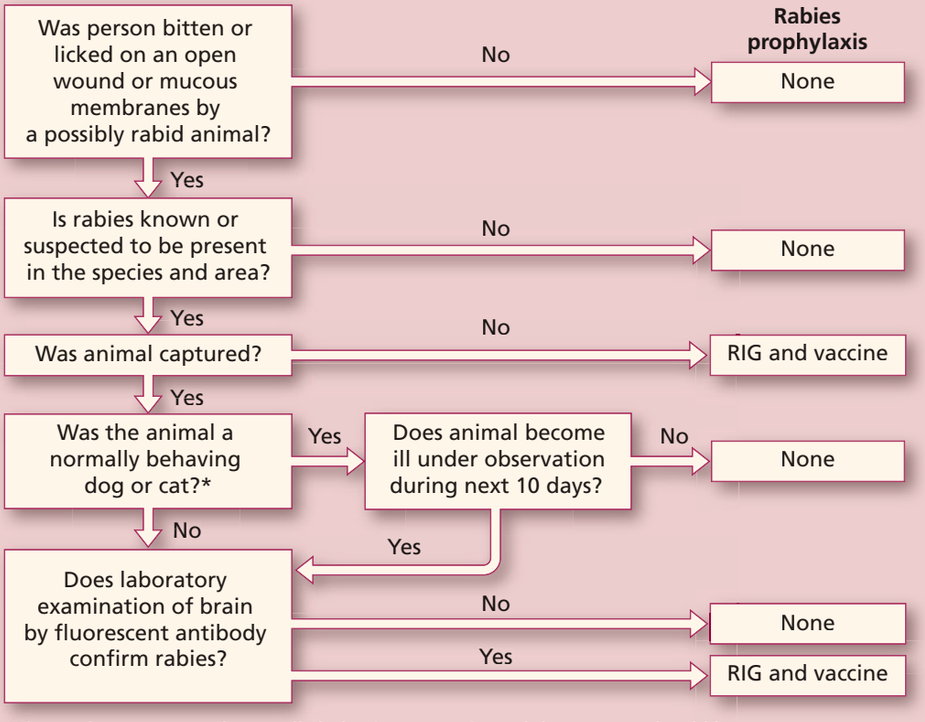


Figure 12-71. Negri body, a cytoplasmic eosinophilic inclusion with central basophilic granules, which is pathognomic of rabies. Unfortunately, these inclusions are present in only 70% to 80% of cases, and might not be seen. The inclusions contain rabies virus antigens. Negri bodies are only found in neurons, most commonly the hippocampal pyramidal cells and cerebellar Purkinje cells, but they may occur in other cortical neurons and other regions of the central nervous system. Perivascular inflammation is mild to minimal, perhaps because rabies virus is transported axonally and transsynaptically, with little extracellular virus extension. A microglial rod cell response usually occurs, as do diffuse degenerative changes of neurons. (*From* Jubelt [31]; with permission.)

Diagnostic Tests for Rabies

- No preclinical diagnostic tests
- CSF—standard viral syndrome
  - Lymphocytic pleocytosis
  - Increased pressure
  - Increased protein level
  - Normal glucose level
- Neck skin biopsy for fluorescent antibody test
  - Need 6–8 mm full-thickness specimen
  - Posterior aspects of neck just above hairline
  - First week of illness 50% positive, greater thereafter
- Corneal impression test—less sensitive, less specific than neck skin biopsy
- Rabies antibody in serum and CSF—high CSF titers seen only in clinical disease
- Culture of rabies virus from saliva, urine sediment, CSF and brain tissue (brain biopsy)

Figure 12-72. Diagnostic tests for rabies. Rabies cannot be diagnosed before the onset of clinical disease. Biopsy of neck skin for fluorescent staining and the cerebrospinal fluid (CSF) antibody (which is not present until at least the second week) and polymerase chain reaction nucleic acid amplification are the most useful diagnostic tests, except for biopsy of the brain. The differential diagnosis includes all causes of encephalitis, both primary and postinfectious. In Australia, the closely related Lyssavirus has caused several cases of fatal encephalitis clinically similar to rabies [48]. Treatable causes such as herpes simplex virus encephalitis are especially important to exclude. Muscular rigidity due to tetanus is also an important differential consideration. Hydrophobia is virtually diagnostic of rabies. In countries where rabies is common, rabies psychosis or hysteria may be seen in those exposed to possibly rabid animals. Paralytic disease caused by poliomyelitis, other enterovirus infections, paralytic zoster, transverse myelitis, and Guillain-Barré syndrome must be excluded.



*Livestock exposure and normally behaving unvaccinated dogs or cats should be considered individually, and local and state public health officials should be consulted.

Figure 12-73. Rabies postexposure prophylaxis algorithm. Over 1 million people in the United States are bitten by animals each year; thus, for each of these bites, a decision must be made about instituting postexposure prophylaxis. Worldwide, dog bites are the main cause of rabies. Fortunately, because of the domestic animal rabies control programs instituted in the 1950s, the chances of getting rabies from a dog in the United States is minimal. RIG—rabies immune globulin. (*Adapted from* Corey [49].)

Postexposure Rabies Prophylaxis Regimen in the United States

	Rabies-naïve Patients	Previously Immunized Patients
Local wound care and passive immunization with rabies antiserum	Cleanse wound with soap and water and a virucidal agent	Cleanse wound with soap and water and a virucidal agent
	HRIG, up to 20 U/kg, with as much as possible by local infiltration into wound; any remaining HRIG given intramuscularly in gluteus or thigh	Administration of HRIG is contraindicated
Active immunization with rabies vaccine	Rabies vaccine, 1-mL dose intramuscularly in deltoid or thigh, × 5 doses (given on days 0, 3, 7, 14, and 28)	Rabies vaccine, 1-mL dose intramuscularly in deltoid or thigh, × 2 doses (given on days 0 and 3)

Figure 12-74. Postexposure rabies prophylaxis regimen. There is no specific treatment for rabies once the clinical disease begins; maximum supportive care in an intensive care unit is the patient's only hope for survival. For individuals at high risk (rabies laboratory workers, some veterinarians, animal control and wildlife workers in endemic areas, and spelunkers and travelers to highly endemic areas in which exposure could occur), pre-exposure prophylaxis should be used. Postexposure prophylaxis includes local wound care, passive immunization with rabies antiserum, and active immunization with rabies vaccine. Both the antiserum and the vaccine should be started immediately. To avoid the formation of antigen-antibody complexes, vaccine and antisera should not be given in the same inoculation or even inoculated into the same geographic site. If human rabies immune globulin (HRIG) is not available, equine antirabies serum can be used, but serum sickness may result. The three rabies vaccines (human diploid cell vaccine [HDCV], rabies vaccine absorbed, and purified chick embryo cell) are equally effective and safe; severe reactions are rare. There have been three cases of recovery from rabies; these patients were treated ineffectively with pre-exposure or postexposure prophylaxis with the older nonhuman rabies animal vaccines before the onset of clinical disease. Rabies postexposure prophylaxis with HRIG and HDCV (or rabies vaccine) has been 100% effective in the United States. Case reports of failure from outside the United States may relate to the use of inappropriate inoculation sites and failure to treat the wound adequately. (*Adapted from* Centers for Disease Control and Prevention [50].)

Postinfectious Encephalitis

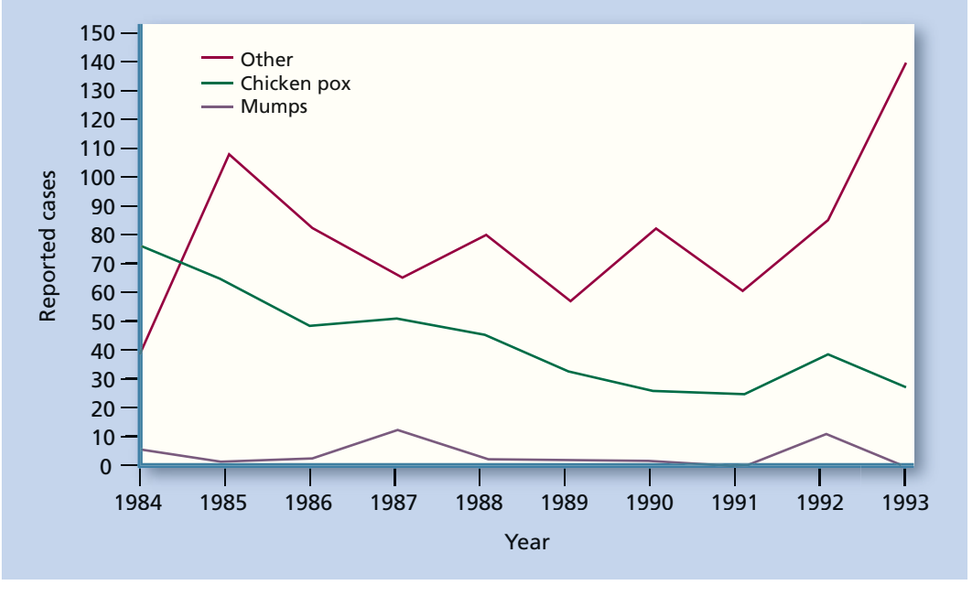


Figure 12-75. Incidence of postinfectious encephalitis (PIE) in the United States from 1984 to 1993. PIE is secondary encephalitis in which an immune-mediated attack appears to be mounted against central myelin. At times the spinal cord is also involved, causing encephalomyelitis. Presumably virus does not need to invade the central nervous system to cause the syndrome, as the immune system can become sensitized to myelin peripherally by sequence homology between viral proteins and myelin proteins. The common causes of PIE are chickenpox (varicella), mumps, and nonspecific upper respiratory infections. Usually this syndrome begins 3 days to 3 weeks after onset of the preceding infection. PIE occurs in cerebral and cerebellar forms. Clinically the cerebral form looks like primary encephalitis (*see* Fig. 12-57). The acute cerebellar ataxic form is the type most often caused by chickenpox and has a good prognosis. Between 100 to 200 cases are reported annually in the United States. (*Adapted from* Centers for Disease Control and Prevention [51].)

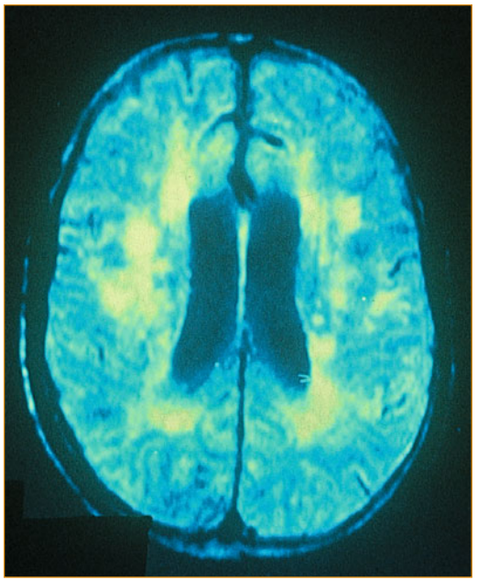


Figure 12-76. Proton-density MRI scan showing demyelination in postinfectious encephalitis (PIE) that occurred 2 weeks after a nonspecific upper respiratory infection. The best diagnostic test for PIE is MRI, which demonstrates white matter disease. Whether the form is cerebral or cerebellar, the cerebrospinal fluid (CSF) profile is similar to that of other acute viral syndromes, with lymphocytic pleocytosis, normal glucose level, elevated protein level, and pressure. One CSF test that may be helpful is the myelin basic protein level, which is usually elevated; unfortunately, in most places, it takes 1 to 2 weeks to receive results. Treatment should be started once the diagnosis is made based on the clinical presentation, including causative disease, a CSF picture consistent with encephalitis, and a positive MRI scan. Treatment consists of high-dose intravenous steroids (1.0 g methylprednisolone daily for 7 to 10 days) to stop the perivascular demyelination. Plasma exchange and IVIg have also been used for treatment [52]. (*Courtesy of* B. Jubelt, MD.)

Poliomyelitis, Myelitis, and Radiculitis

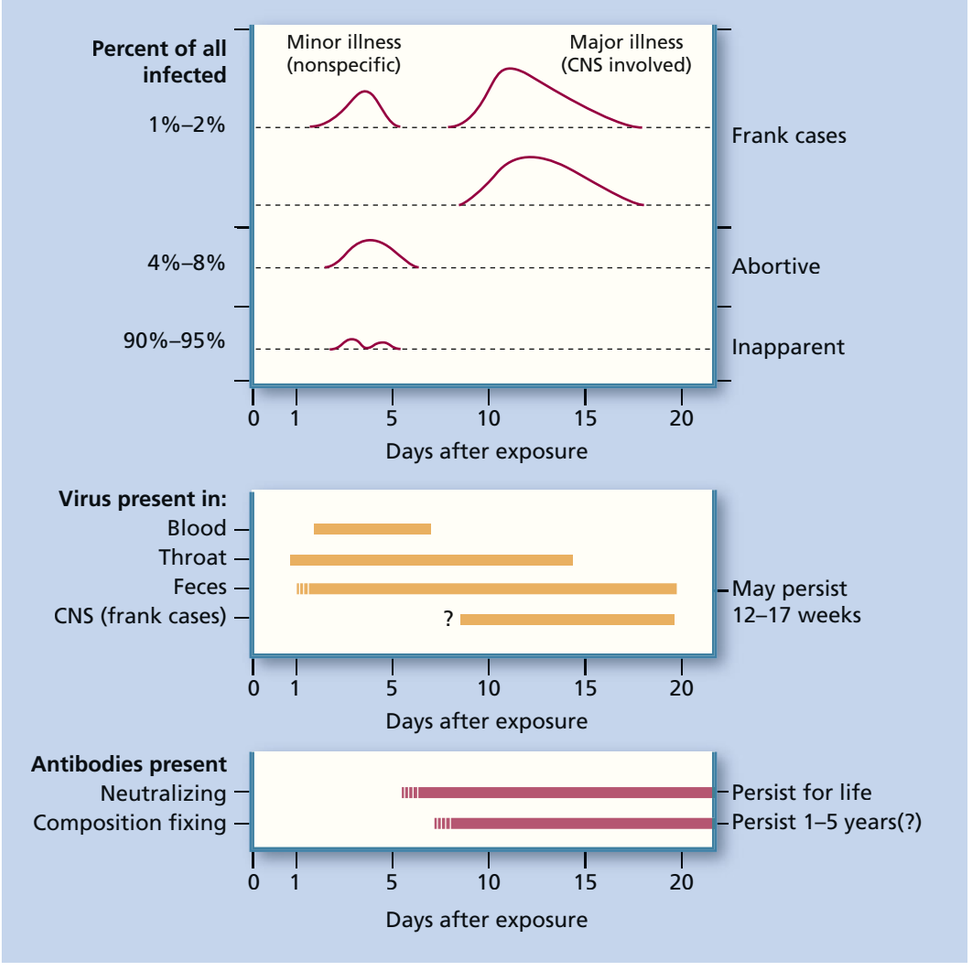


Figure 12-77. Correlation of clinical forms of poliomyelitis with the time of viral replication and antibody production. The term *poliomyelitis* is from the Greek words for gray marrow ("polio") and spinal cord ("myelitis"): "the gray marrow of the spinal cord." Sometimes the term *anterior* is added as a reminder that it is the anterior rather than the posterior horns that are inflamed in poliomyelitis. Only about 1% to 2% of those infected with the virus develop paralysis (major illness) with or without the nonspecific, systemic, febrile minor illness. Paralysis is usually asymmetric and flaccid, and can occur in all four extremities, as well as in the brain stem, causing bulbar polio with cranial nerve palsies, respiratory insufficiency, dysphagia, and coma. The use of oral polio vaccine has eradicated poliomyelitis caused by wild type virus in the United States and other developed countries. Killed polio vaccine is now used in the United States for vaccination. However, poliomyelitis is still a significant problem in underdeveloped areas. CNS—central nervous system. (*Adapted from* Horstmann [53].)

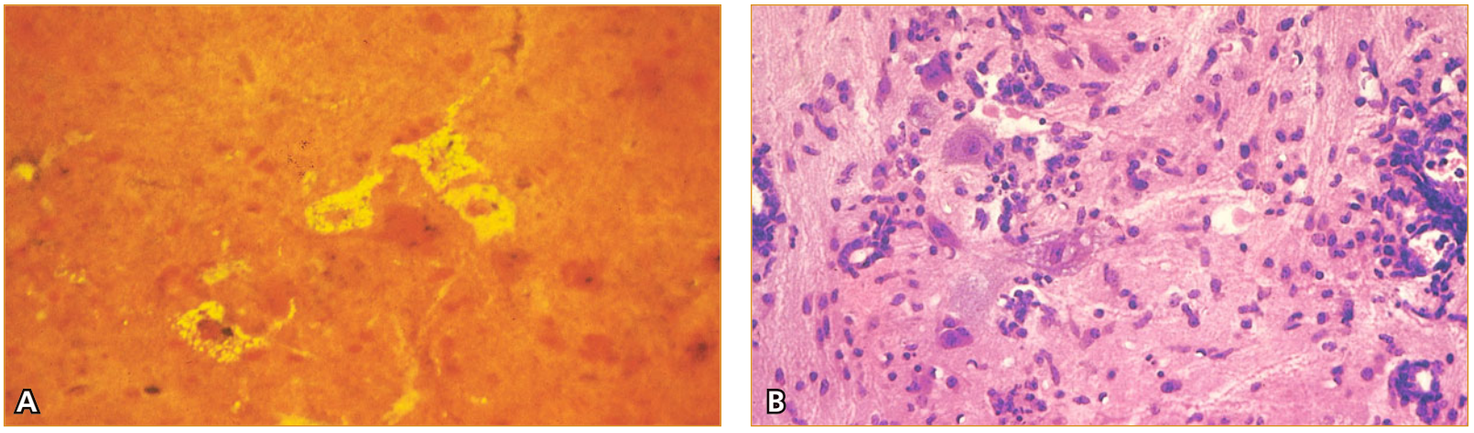


Figure 12-78. Histology slides showing pathogenesis and pathology of poliomyelitis. The paralysis in poliomyelitis is caused by poliovirus infecting the large anterior horn motor neurons. With destruction of these motor neurons, an intense inflammatory response ensues. **A**, Fluorescent antibody staining of type 2 poliovirus antigen in large anterior horn cells of the lumbar spinal cord in a mouse model of human poliomyelitis. Immunofluorescence in the cytoplasm and processes of these cells is prominent. Poliovirus is an RNA virus that replicates in the cytoplasm; therefore there is no immunofluorescence in the nucleus. Adjacent to the infected cells are dark unstained, uninfected neurons. **B**, Cervical cord showing poliomyelitis due to intracerebral injection of Lansing type 2 poliovirus in a mouse model of human poliomyelitis. Anterior horn cells show various stages of neuronal degeneration. The inflammatory response consists of perivascular mononuclear cell cuffing; parenchymal, mononuclear, and microglial cell infiltrates; and neuronophagia. (*From* Jubelt *et al*. [54]; with permission.)

Differential Diagnosis of Poliomyelitis

Non–polio enteroviruses (EV)
- Coxsackieviruses—rare, mild paralysis
- Echoviruses—rare, mild paralysis
- EV 70—severe paralysis in Asia, Africa, Europe; no paralysis in the New World
- EV 71—severe paralysis in Eastern Europe; rare, mild paralysis in the New World
- West Nile virus—acute, flaccid paralysis

Rabies virus—paralytic or "dumb" rabies

Herpes zoster—"zoster paresis"

Guillain-Barré syndrome—usually symmetric

Botulism—symmetric

Acute toxic neuropathies—symmetric with stocking/glove sensory loss

Acute intermittent porphyria—symmetric paralysis, psychiatric symptoms, delirium, abdominal pain, seizures

Acute transverse myelitis—usually symmetric with sensory level and bowel and bladder involvement

Cord compression from epidural abscess—same as transverse myelitis, also localized back percussion tenderness

Figure 12-79. Differential diagnosis of poliomyelitis. The diagnosis of poliomyelitis is based on the clinical paralysis, the cerebrospinal fluid profile picture of an acute viral syndrome, isolation of virus from the throat or stool, and a fourfold rise in the serum antibody level. The differential diagnosis includes other causes of acute lower motor neuron flaccid paralysis. Paralysis is usually asymmetric, without bladder or sensory involvement. Bladder and sensory involvement, however, resulting in a picture of transverse myelitis, has been caused by poliovirus, thus expanding the differential diagnosis to this entity. The only specific treatment for poliomyelitis is prevention with poliovirus vaccine. Both the live attenuated oral vaccine (Sabin type) and the inactive injectable vaccine (Salk type) are used throughout the world. Treatment of the acute disease is supportive.

Acute Transverse Myelitis

Viruses Causing Acute Transverse Myelitis*

Common	Uncommon	Rare
Herpes simplex virus type 2	Mumps	Poliovirus
Cytomegalovirus	Influenza	Coxsackievirus
Varicella-zoster virus	Rubella	Echovirus
Epstein-Barr virus		Rabies
		Hepatitis A and B
		Measles

**Viruses causing encephalomyelitis, in which myelitis occurs only with encephalitis, are not listed.*

Figure 12-80. Viruses causing acute transverse myelitis. The syndrome of "acute transverse myelitis" consists of acute flaccid paralysis with hypoflexia (later may develop spasticity with hyperreflexia), sensory loss usually with a sensory level, and bowel and bladder involvement. The paralysis is symmetric and thus different from the usual asymmetric paralysis seen in poliomyelitis. In addition to viruses, this clinical syndrome may be caused by cord compression from epidural abscess or epidural tumor that hemorrhages; intraspinal abscess or intraspinal hemorrhaging tumor; spinal cord infarct; vasculitis (*eg*, systemic lupus erythematosus) causing infarction; postinfectious immune-mediated myelitis; multiple sclerosis; and remote effects of cancer. Treatment consists of the use of a specific viral agent when the agent is identified with our without high-dose intravenous methylprednisolone [55].

Cytomegalovirus Polyradiculitis

Cytomegalovirus Neurologic Infections

Disease and Features	Host and Frequency
Cytomegalic inclusion body disease	Neonate, congenital disease—rare
Encephalitis	
Microencephaly	
Seizures	
Mental retardation	
Periventricular calcifications	
Disseminated disease	
Encephalitis/ventriculitis	Immunocompromised patient (described primarily in AIDS patients)—uncommon
Subacute course (1–3 mo)	
Progressive mental status changes	Immunocompromised patient—rare
Disseminated disease in the immunocompromised patient	
MRI—periventricular hyperintensities, meningeal enhancement	
Polyradiculitis/polyradiculomyelitis	Immunocompromised patient (described only in AIDS patients)—common
Pain and paresthesia in legs and perineum	
Sacral hypesthesia	
Urinary retention	
Subacute ascending hypotonic paraparesis	
Eventually ascend to cause myelitis	
CSF—pleocytosis (PMNs > lymphocytes), low glucose level, high protein level, CMV positive by culture or PCR	
Usually disseminated disease	
MRI—lumbosacral leptomeningeal enhancement	
Multifocal neuropathy	Immunocompromised patient (described only in AIDS)—uncommon
Markedly asymmetric	
Numbness, painful paresthesia for months, followed by sensorimotor neuropathy	
Usually disseminated disease	
CMV positive in CSF by culture or PCR	

Figure 12-81. Cytomegalovirus (CMV) neurologic infections. Prior to the occurrence of the AIDS epidemic in the United States, CMV was known primarily for causing cytomegalic inclusion body disease, an infrequent congenital disease of newborns. Cases of CMV encephalitis have been recognized rarely in immunocompetent individuals. CMV ventriculitis and encephalitis occur most often as an opportunistic infection in AIDS patients. The most common syndrome caused by CMV today, however, is the CMV polyradiculitis (polyradiculopathy)/polyradiculomyelitis (polyradiculomyelopathy). This syndrome occurs relatively late in the course of AIDS when the $CD4^+$ T-lymphocyte count is usually less than 100. Less frequent and also late in the course of AIDS is CMV multifocal neuropathy. Ganciclovir and foscarnet have been reported to be beneficial in some postnatally acquired infections [56]. CSF—cerebrospinal fluid; PCR—polymerase chain reaction; PMNs—polymorphonuclear leukocytes.

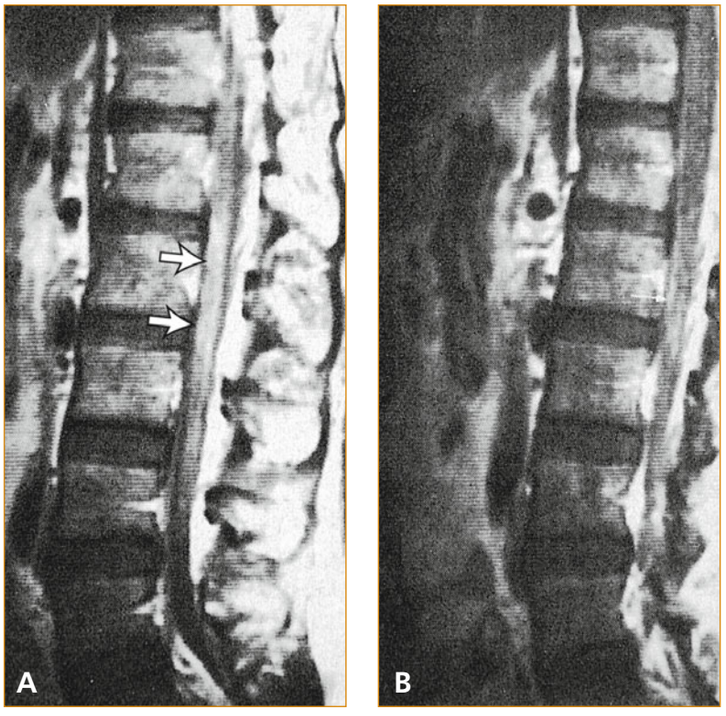
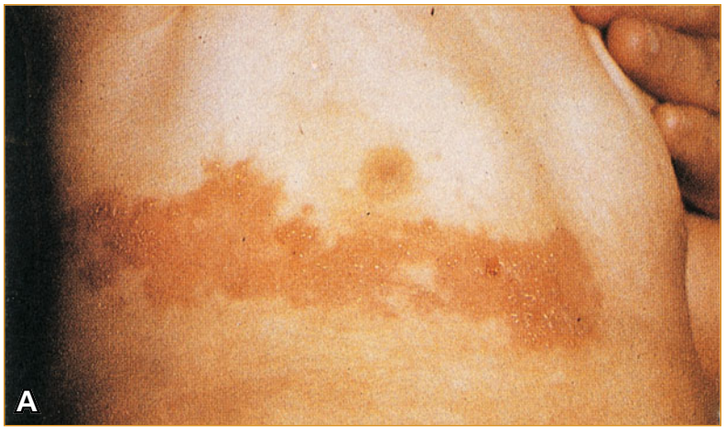


Figure 12-82. Enhanced T1-weighted sagittal magnetic resonance image of nerve roots from L1 to L4 and the cauda equina region (*arrows*) in a patient with cytomegalovirus polyradiculitis/polyradiculomyelitis (**A**). In the right half of the picture, the pial lining of the sac is also enhanced. Usually these lesions are visible only with enhancement (**B**). (*From* Talpes *et al*. [57]; with permission.)

Herpes Zoster



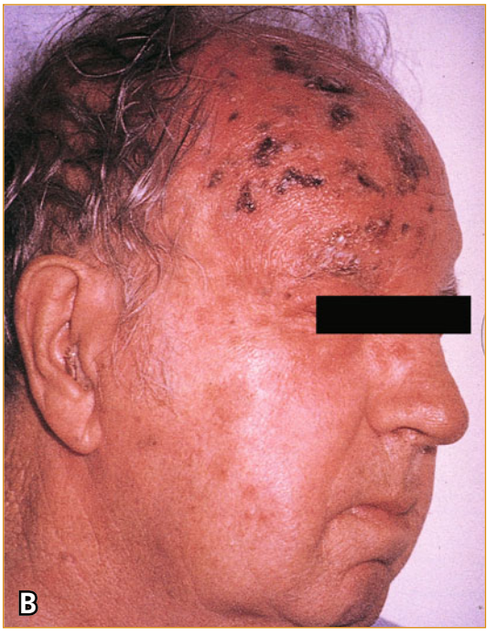


Figure 12-83. Herpes zoster. Herpes zoster is a distinctive syndrome caused by the varicella-zoster virus (VZV), which also causes chickenpox (varicella). The chickenpox virus travels from the skin up the sensory nerves to become latent in the dorsal root ganglia. Later in life, the virus reactivates, replicates in the ganglia, and travels down the nerve to the skin to cause a dermatomal vesicular eruption. The incidence of zoster increases with age and is more common in those with compromised cellular immunity. Typically, patients experience dermatomal paresthesia or dysesthesias (itching, burning pain, tingling) for 1 to 2 days, after which the vesicular eruption occurs. Most patients have hypalgesia and hypesthesia in the affected dermatome. **A**, Herpes zoster in a thoracic dermatome. **B**, Herpes zoster ophthalmicus. Herpes zoster of the ophthalmic division of the trigeminal nerve. (**A**, *from* Murray *et al*. [58]; with permission; **B**, *from* Rosencrance [59]; with permission.)

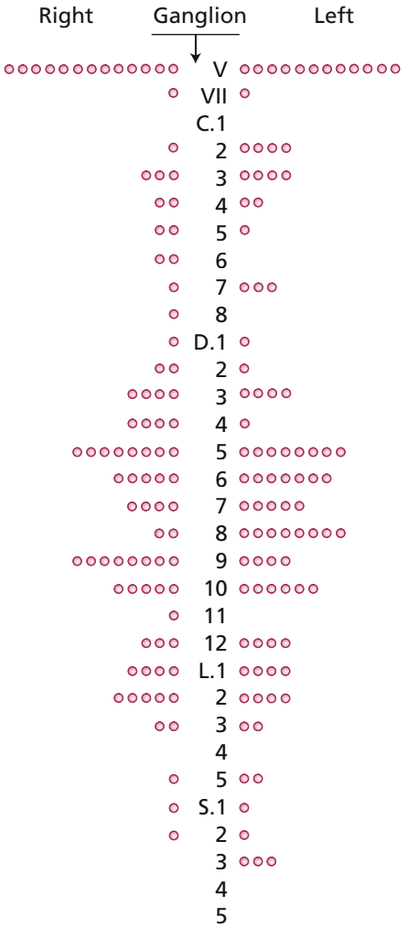


Figure 12-84. Segmental distribution of herpes zoster. Most cases occur in the thoracic nerves, the lumbar nerves, and the ophthalmic divisions of the trigeminal nerve (ophthalmic zoster). Approximately 40% to 50% of patients younger than 50 years of age develop postherpetic neuralgia (PHN), which is pain persisting for more than 6 weeks after the rash clears. The pain can be severe. PHN can be helped with amitriptyline and carbamazepine; local application of capsaicin may also help. For patients over 50 years of age, the use of oral acyclovir seems prudent in the hope of preventing PHN. Complications of herpes zoster include zoster paresis, myelitis, encephalitis, disseminated disease, and infection of the eye. Secondary to ophthalmic zoster (*see* Fig. 12-83**B**) are keratitis, conjunctivitis, ocular muscle palsies, ptosis, mydriasis, contralateral hemiplegia due to viral spread to the ipsilateral carotid or middle cerebral artery, and the Ramsay Hunt syndrome (geniculate zoster, herpes zoster oticus) with facial palsy, loss of taste, and vesicles in the external auditory meatus. Intravenous acyclovir is indicated for disseminated zoster and probably for most of these complications, although controlled studies of its use for complications have not been reported. A recent study using a highly potent varicella vaccine reduced the incidence of zoster (shingles) by 51% and postherpetic neuralgia by 66.5%. Of those who did developed shingles, the vaccine significantly reduced morbidity [60]. (*Adapted from* Hope-Simpson [61].)

Slow or Chronic Viral Infections

Slow Viral Infections of the Central Nervous System

- Conventional viruses
  - Retroviruses
    - AIDS
    - HTLV-1–associated myelopathy/tropical spastic paraparesis
  - Progressive multifocal leukoencephalopathy
  - Subacute sclerosing panencephalitis
  - Subacute measles encephalitis
  - Progressive rubella panencephalitis
  - Enteroviruses—polioviruses, echoviruses
  - Other—cytomegalovirus, adenovirus
- Prion diseases (spongiform encephalopathy agents)
  - Kuru
  - Creutzfeldt-Jakob disease
  - Gerstmann-Sträussler syndrome
  - Fatal familial insomnia

Figure 12-85. Slow viral infections of the central nervous system (CNS). Slow or chronic viral infections that result in chronic neurologic disease are caused by both conventional viruses and the prion agents. Prion agents (unconventional transmissible spongiform encephalopathy agents) are not true viruses and are reviewed in the next section. The conventional viruses are true viruses with RNA or DNA genetic material and a recognizable structure on electron microscopy. Slow infections to be reviewed in detail are caused by retroviruses (AIDS, human T-cell lymphotropic virus [HTLV]-1–associated myelopathy/tropical spastic paraparesis), papovaviruses (progressive multifocal leukoencephalopathy), and measles virus (subacute sclerosing panencephalitis [SSPE]).

Subacute measles encephalitis (SME) has also been referred to as "immunosuppressive measles encephalitis" and "measles inclusion body encephalitis" because of the large number of Cowdry type A intranuclear inclusions present. SME occurs most often in children immunosuppressed with chemotherapy for lymphoma or leukemia. A few cases have occurred in adults. The incubation period is less than 6 months from the time of measles exposure. Clinical manifestations are seizures, hemiparesis, retinitis, and cortical blindness followed by coma and death in weeks to months. There is no treatment. The cerebrospinal fluid (CSF) is usually normal except for increased measles antibody titers. The electroencephalogram (EEG) may reveal focal slowing but no periodic complexes. Because of the immunosuppressed state, a large load of virus appears to reach the CNS.

Continued on the next page

Figure 12-85. *(Continued)* Progressive rubella panencephalitis was recognized as a distinct disease entity in 1974, at which time only several dozen cases had been reported. The disease develops during adolescence, usually in patients having stigmata of congenital rubella. Clinically the disease resembles SSPE in onset with dementia. Myoclonus and seizures are less prominent than in SSPE, but cerebellar ataxia is more prominent. The course is protracted over 8 to 10 years to death. There is no treatment. High levels of rubella antibody appear in the serum and CSF. Both CSF protein and IgG are increased, oligoclonal bands are present, and some patients have CSF pleocytosis (10 to 40 monocytes/mm^3). The EEG reveals diffuse slowing (rarely periodicity). Persistent infection is believed to cause the formation of immune complexes that are deposited in vessel walls, causing vasculitis.

Persistent enterovirus infections in agammaglobulinemic children have been caused by both attenuated polioviruses (vaccine strains) and echoviruses. The illness caused by polioviruses consists of a course of 2 to 3 months with both diffuse encephalitis and lower motor neuron paralysis. In the echovirus infections, the course may last months to several years with just encephalitis. About half the patients, however, have a polymyositis-like syndrome from echoviral infection of muscles. These patients may have remissions with intrathecal administration of antibodies, although as yet there are no definite cures. As previously noted (*see* Fig. 12-81), cytomegalovirus can cause subacute to chronic infections in AIDS patients, as can adenovirus, but less frequently.

AIDS

Neurologic Syndromes in Patients with HIV Infection

Syndrome	HIV Related	Opportunistic Process
Leptomeningeal disease	Acute, aseptic meningitis	Other viruses: HSV, VZV, EBV, CMV, hepatitis B
	Chronic meningitis	Fungal: primarily *Cryptococcus**
		Bacterial: syphilis, mycobacteria*, listeriosis, pyogenic bacteria
		Lymphomatosis meningitis
Cerebral syndromes	Acute HIV encephalopathy*	Toxoplasmosis*
	Chronic HIV-encephalopathy/encephalitis (AIDS dementia complex)	CMV encephalitis*
		HSV encephalitis
		PML*
		Abscesses; bacterial, fungal
		Diffuse atypical mycobacterium*
		Primary central nervous system lymphoma*
		Metastatic lymphoma* Kaposi's sarcoma*
Spinal cord syndromes	HIV vacuolar myelopathy	Viral myelitis: HSV, VZV, CMV
	Anterior horn cell disease	CMV anterior horn cell disease?
		HAM/TSP
Cranial neuropathies	Immune-complex retinopathy	CMV, toxoplasmosis, and *Candida* retinitis
	Others secondary to meningitis	Others secondary to meningitis
Peripheral neuropathies	Predominantly sensory polyneuropathy	CMV polyradiculitis
	Acute and chronic inflammatory demyelinating polyneuropathies	CMV mononeuritis multiplex
	Mononeuritis multiplex	
Muscle disease	HIV myopathy	*Toxoplasma* myositis

**AIDS indicator diseases.*

Figure 12-86. Major neurologic syndromes in patients with HIV infection. The various neurologic syndromes occurring in HIV-infected patients are caused by the direct effects of HIV or opportunistic processes. CMV—cytomegalovirus; EBV—Epstein-Barr virus; HAM/TSP—HTLV-1–associated myelopathy and tropical spastic paraparesis; HSV—herpes simplex virus; PML—progressive multifocal leukoencephalopathy; VZV—varicella-zoster virus.

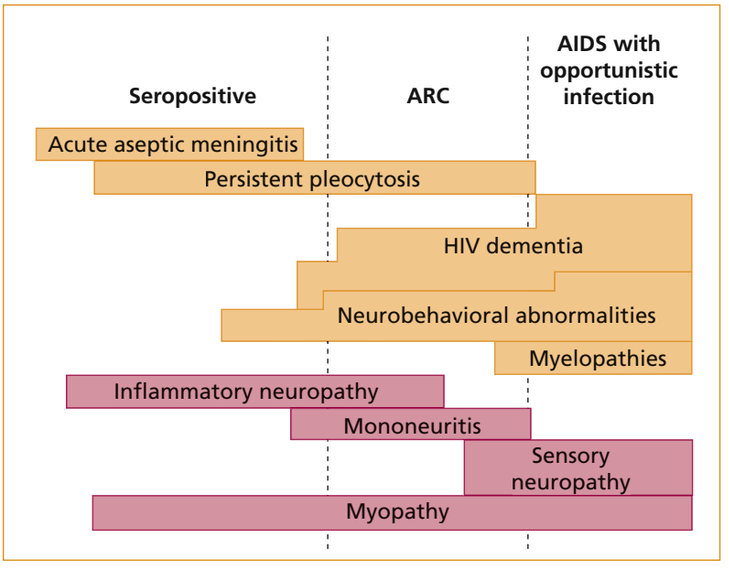


Figure 12-87. Timing and relative frequency of neurologic complications due to the direct effects of HIV infection. Diseases that affect the central nervous system are shaded in *orange*, whereas those affecting the peripheral nervous system are shaded in *pink*. The relative frequency of each complication is indicated by the height of each box. No clinical or cerebrospinal fluid (CSF) features distinguish HIV acute aseptic meningitis from other viral meningitides, but the HIV p24 core protein and HIV antibody are often found in the CSF. The chronic persistent pleocytosis is more often asymptomatic than symptomatic. As noted in Figure 12-86, both acute and chronic demyelinating polyneuropathies (AIDP, CIDP) may occur, which are clinically similar to non-HIV AIDP (Guillain-Barré syndrome) and CIDP. Usually, however, a CSF pleocytosis appears rather than the typical albumino-cytologic dissociation. Treatment is plasmapheresis or intravenous administration of immunoglobulins.

As the HIV infection progresses, patients become symptomatic with neurobehavioral abnormalities and dementia (HIV encephalopathy), also referred to as the AIDS dementia complex. At approximately the same time, a mononeuritis multiplex may occur, which is thought to be due to ischemic injury. It must be distinguished from cytomegalovirus (CMV) mononeuritis multiplex.

Late in the course of infection when patients have met the criteria for the diagnosis of AIDS (less than 200 $CD4^+$ T lymphocytes or the occurrence of indicator diseases), opportunistic infections are more likely to occur, but HIV also causes several syndromes. One is the chronic vacuolar myelopathy that results in corticospinal tract and posterior column sensory signs (vibration and position sense loss). It needs to be distinguished from secondary human T-cell lymphotropic virus-1–associated myelopathy/tropical spastic paraparesis. Other viral myelitides are too acute (herpes simplex virus, varicella-zoster virus) or subacute (CMV) to fit the picture. Also, distal, primarily sensory polyneuropathy may occur, which is the most common neuropathy to appear late in the disease, occurring in about a third of AIDS patients. The neuropathy is painful and there is loss of pain sensation, temperature sensation, light touch, and reflexes. CMV polyradiculitis is the primary differential diagnosis. An HIV myopathy may also be seen but is infrequent; a myopathy secondary to zidovudine therapy is more likely. ARC—AIDS-related complex. (*Adapted from* Johnson *et al*. [62].)

A Early Manifestations of the AIDS Dementia Complex

Symptoms	Signs
Cognition	Mental status
Impaired concentration	Psychomotor slowing
Forgetfulness	Impaired serial 7s or reversals
Mental slowing	Organic psychosis
Motor	Neurologic examination
Unsteady gait	Impaired rapid movements (limbs, eyes)
Leg weakness	Hyperreflexia
Loss of coordination, impaired handwriting	Release reflexes (snout, glabellar, grasp)
Tremor	Gait ataxia (impaired tandem gait, rapid turns)
Behavior	Tremor (postural)
Apathy, withdrawal, personality change	Leg weakness
Agitation, confusion, hallucinations	

B Late Manifestations of AIDS Dementia Complex

Mental Status	Neurologic Signs
Global dementia	Weakness (legs, arms)
Psychomotor slowing: verbal responses delayed, near or absolute mutism, vacant stare	Ataxia
Unawareness of illness, disinhibition	Pyramidal tract signs: spasticity, hyperreflexia, extensor plantar responses
Confusion, disorientation	Bladder and bowel incontinence
Organic psychosis	Myoclonus

Figure 12-88. Clinical features of HIV encephalopathy (AIDS-dementia complex). **A**, In the early manifestation of AIDS dementia, HIV encephalopathy presents as a subcortical white matter disconnection syndrome with psychomotor slowing and impaired concentration. Gait ataxia is also a common early sign. **B**, In the late manifestations, AIDS dementia becomes global and psychomotor slowing severe. Patients often do not speak spontaneously and exhibit a delayed response to questions. (*Adapted from* Price *et al*. [63].)

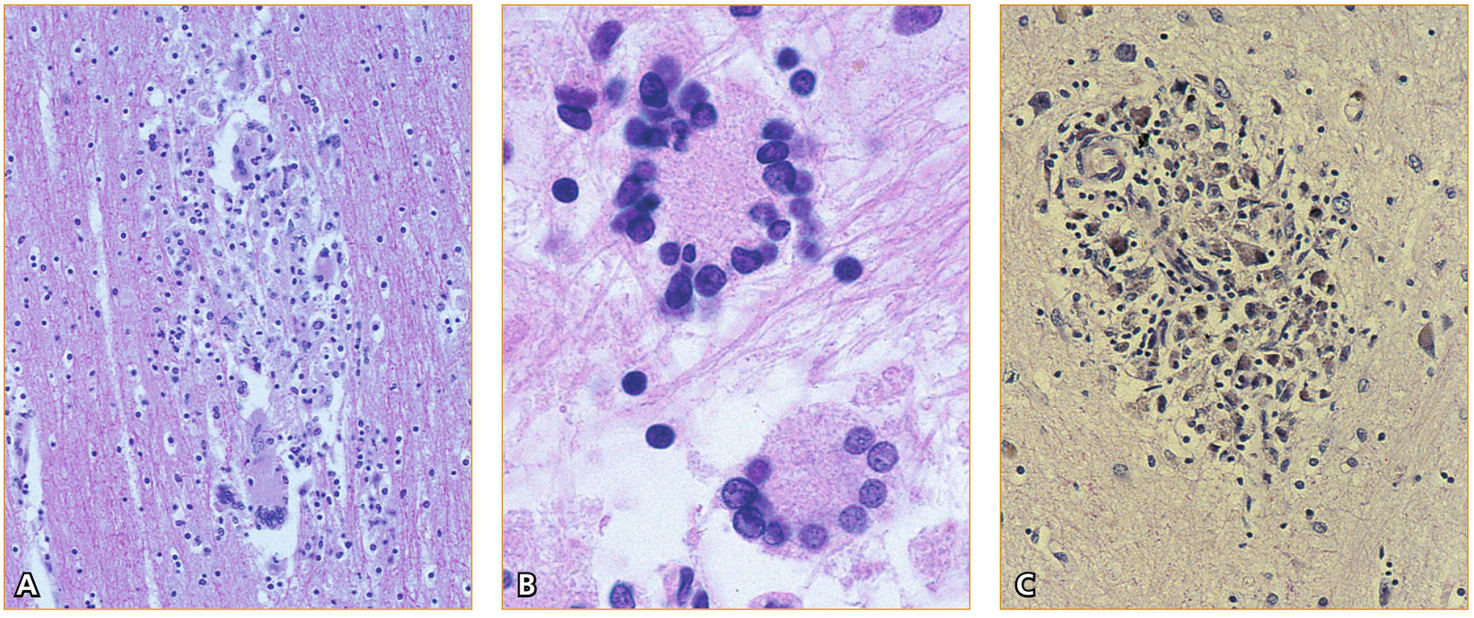


Figure 12-89. Pathology of HIV encephalopathy. The hallmarks of HIV encephalopathy are the multinucleated giant cells and microglial nodules. These cells appear throughout the cortex and white matter and are infected with HIV. HIV antigen is also found in glia and endothelial cells, but not neurons. Therefore, neuronal dysfunction is not the result of viral replication, and has not been clarified. **A**, Focal area of inflammation with a multinucleated giant cell and tissue disruption in HIV encephalopathy. Lesions are usually composed of macrophages and microglia. **B**, Multinucleated giant cells of macrophage origin. These cells appear to be the result of syncytial fusion of HIV-infected macrophages and microglia. **C**, Microglial nodule composed of macrophages and microglia. (*From* Hanley *et al*. [36].)

Differential Diagnosis of HIV Encephalopathy and Common Complications of AIDS

		Clinical Manifestations			Neuroimaging Findings		
Disorder	**Approximate Incidence, %**	**Onset**	**Alertness**	**Features**	**Lesions, *n***	**Type of Lesions**	**Location of Lesions**
AIDS dementia (HIV) encephalopathy	67	Weeks to months	Preserved	Personality change, unsteady gait, seizures, dementia	None, multiple, or diffuse	Increased MRI T2 signal, no enhancement or mass effect	White matter, basal ganglia
Cerebral toxoplasmosis	15	Days	Reduced	Fever, headaches, focal deficits, seizures	Multiple	Multiple, low-density ring-enhancing lesions on CT and T1-weighted MRI; spherical, increased T2-weighted MRI signal; mass effect	Cortex, basal ganglia
Cryptococcal meningitis	~ 9	Weeks	Variable	Fever, headaches, nausea and vomiting, confusion	None, hydrocephalus	—	—
Progressive multifocal leukoencephalopathy	4	Weeks	Preserved	Multiple focal deficits, late dementia	Multiple	Multiple, diffuse nonenhancing; no mass effect	White matter, adjacent to cortex
Primary central nervous system lymphoma	1	Days to weeks	Variable	Headache, focal deficits, seizures	One or few	Single > multiple; diffuse > ring enhancement; mass effect	Periventricular, white matter

Figure 12-90. Differential diagnosis of HIV encephalopathy and common complications of AIDS. By the end of 2005, over 1 million cumulative cases of AIDS had been reported to the Centers for Disease Control and Prevention (CDC) from the United States and its territories. Of these cases 62% of patients had died. The World Health Organization estimates that there have been 40 million cases worldwide. It is estimated that about two thirds of AIDS patients develop HIV encephalopathy. The figure lists the common complications of AIDS. Obviously less frequent complications such as bacterial brain abscesses (less than 1%), tuberculous meningitis with hydrocephalus and infection (1%), and other encephalitides (herpes simplex virus, varicella-zoster virus, and cytomegalovirus) may be part of the differential diagnosis at times. (*Adapted from* Price *et al*. [63] and Fauci and Lane [64].)

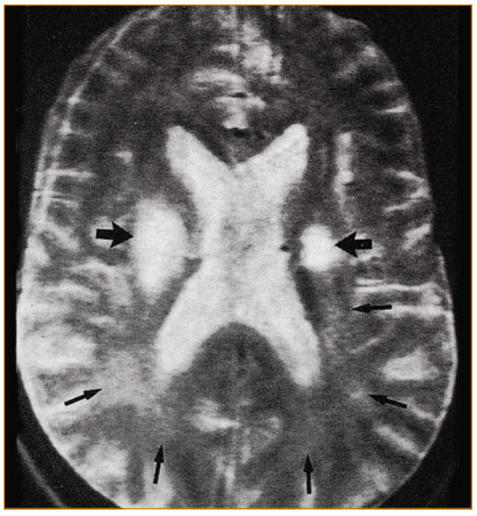


Figure 12-91. T2-weighted MRI scan showing bilateral diffuse (*small arrows*) and patchy white matter lesions (*large arrows*) in the brain of an AIDS patient. CT scans of HIV encephalopathy are nonspecific and only reveal diffuse atrophy with diffuse cortical atrophy and enlarged ventricles. T1-weighted MRI scans will also reveal diffuse atrophy. On T2-weighted MRI scans, in addition to atrophy, increased signal in the white matter is seen in 25% to 30% of AIDS patients. These changes may be diffuse or may be focal, patchy, or punctate. (*From* Olsen *et al.* [65], with permission.)

AIDS Chemotherapeutic Agents—2007

Generic Name*	Abbreviation	Common Side Effects
Nucleoside reverse transcriptase inhibitors (NRTIs)		
Zidovudine	AZT, ZDV	Bone marrow suppression, hepatitis, GI upset, myopathy
Didanosine	ddI	Painful sensory neuropathy, pancreatitis, diarrhea
Stavudine	d4T	Painful sensory neuropathy, hepatitis
Lamivudine	3TC	Bone marrow suppression, GI upset
Abacavir	ABC	Hypersensitivity reactions, GI upset
Adefovir	ADV	GI upset, hepatic and renal toxicity
Emtricitabine	–	Headache, GI upset, rash
Protease inhibitors (PIs)		
Saquinavir	SQV	Diarrhea, abdominal pain
Ritonavir	RTV	GI upset, diarrhea, fatigue, circumoral paresthesias
Indinavir	IDV	GI upset, diarrhea, kidney stones, hyperbilirubinemia
Nelfinavir	NFV	Diarrhea
Amprenavir	141W94	Rash (including Stevens-Johnson), GI upset, headache
Lopinavir	–	Pancreatitis, diarrhea
Fosamprenavir	–	GI upset, diarrhea, headache, rash
Atazanavir	ATV	Rash (including Stevens-Johnson), hyperbilirubinemia, GI upset
Tipranavir	TPV	GI upset, diarrhea, fatigue, headache, rash, pyrexia
Darunavir	TMC114	GI upset, headache, nasopharyngitis
Nonnucleoside reverse transcriptase inhibitors (NNRTIs)		
Nevirapine	NVP	Hepatitis, rash, headache
Delavirdine	DLV	Rash
Efavirenz	EFV	Encephalopathy (25% transient, 3% limiting), hepatitis, rash
Nucleotide analogue reverse transcriptase inhibitors (NTRTIs)		
Tenofovir	–	Hepatitis, rash, headache
Fusion inhibitors		
Enfuvirtide	T20	Injection site reaction, diarrhea, fatigue, pneumonia

**Combination drugs are not shown.*

Figure 12-92. Treatment of HIV encephalopathy and other syndromes caused by the direct effects of HIV infection. Specific antiretroviral agents can be used for all syndromes caused directly by HIV. Over 20 drugs in five classes have been approved for HIV treatment. Specific agents for the treatment of HIV infections include nucleoside reverse transcriptase inhibitors (NRTIs), protease inhibitors (PIs), nonnucleoside reverse transcriptase inhibitors (NNRTIs), nucleotide analogue reverse transcriptase inhibitors (NTRTIs), and fusion inhibitors. Therapy is recommended for all patients with symptomatic established HIV infection. Combination therapy is used. Initial regimens of two NRTIs plus either a PI or an NNRTI boosted with low-dose ritonavir is recommended [66]. Both $CD4^+$ cell and HIV RNA levels are used to decide when to start and change therapy [66]. Triple combination therapies with RTIs and a PI or an NNRTI have been referred to as highly active antiretroviral therapy [66]. When prescribing anti-HIV therapy, it is important to know the interactions between these agents as well as the interactions between these agents and other medication classes (antihistamines, antifungals, antimycobacterials, oral contraceptives, cytochrome P450 metabolized drugs, benzodiazepines, antibiotics, methadone, anticonvulsants, antiarrhythmics, calcium channel blockers, and ergot alkaloids).

Symptomatic treatment such as antidepressants or antipsychotics for HIV encephalopathy may be useful. For the painful sensory neuropathy, analgesics, antidepressants (especially tricyclics), anticonvulsants (carbamazepine, phenytoin), and topical capsaicin ointment may be helpful. GI—gastrointestinal.

HTLV-1–Associated Myelopathy/Tropical Spastic Paraparesis

Figure 12-93. Neurologic signs of human T-cell lymphotropic virus (HTLV)-1–associated myelopathy and tropical spastic paraparesis (HAM/TSP). HAM/TSP is characterized by a chronic progressive spastic paraparesis, usually with a neurogenic bladder. Patients may have paresthesia and pain in the legs. Both posterior column and spinothalamic sensory loss have been seen but usually in a minority of cases. Infrequently, cranial nerve (CN) signs are seen, with optic atrophy the most common. Other CN signs include nystagmus, diplopia, deafness, and facial paresis. Antibodies to HTLV-1 have been found in 80% to 100% of cases, and HTLV-1 has been isolated from the cerebrospinal fluid. The pathogenesis appears more likely to be an immune-mediated process, as cytotoxic T lymphocytes rather than HTLV-1 viral titer levels are related to the demyelinating lesions. Pathologic changes include inflammation of the leptomeninges, perivascular cuffing, and inflammation of the cord parenchyma. Symmetrical demyelination of the corticospinal tracts occurs, and to a lesser degree and frequency, demyelination of the posterior columns and spinothalamic and spinocerebellar tracts. Much less frequently, patients with HTLV-1 infections have presented with an ALS-like picture, polyneuropathy, and inflammatory and noninflammatory myopathies [67].

Most cases of HAM/TSP occur in warm areas along the equator, where the virus is endemic. Isolated cases have occurred in more northern and southern latitudes, including northern areas of the United States. The disease usually begins in the third or fourth decade and women are more commonly affected, with a female to male ratio of about 2 to 1. The virus appears to be transmitted by vertical transmission from the mother to the infant through breastfeeding, sexual contact, intravenous drug use, and blood transfusions. For cases reported from the United States, except for the endemic area of South Florida, 20% to 25% of the time the mode of transmission cannot be determined. (*Adapted from* Rodgers-Johnson *et al*. [68].)

Neurologic Signs of HAM/TSP

Abnormal Signs	Affected, %
Corticospinal signs	
Legs	
Spasticity	100
Weakness	90–100
Arms	
Spasticity	60–90
Weakness	20–50
Increased jaw jerk	30–70
Bladder dysfunction	70–90
Impaired position, vibration sense	10–60
Root or cord sensation	20–65
Optic atrophy	2–20
Cerebellar signs	3–10

Figure 12-94. Differential diagnosis of human T-cell lymphotropic virus (HTLV)-1–associated myelopathy and tropical spastic paraparesis (HAM/TSP). The differential diagnosis of HAM/TSP is that of a chronic spastic progressive paraparesis. The diagnosis can be made by analysis of the cerebrospinal fluid (CSF). Less than half of patients have mild pleocytosis, while more than half have an elevated protein level. Specific CSF tests include the presence of HTLV-1 antibody and HTLV-1 oligoclonal bands, virus isolation from the CSF, and the detection of the HTLV-1 genome using polymerase chain reaction amplification. MRI may reveal nonspecific demyelination in the spinal cord and brain. For treatment, prednisone and danazol have been reported to be beneficial but have not been tested in a controlled fashion. In a recent double-blind, controlled study, however, two thirds of the patients reported a benefit from 3.0 million units per day of interferon-α. (*Adapted from* Izumo *et al*. [69].)

Differential Diagnosis of HAM/TSP

- Cervical or thoracic cord compression
  - Chiari malformations
  - Foramen magnum tumors
  - Cervical spondylosis
  - Cervical and thoracic herniated discs
  - Arteriovenous malformations
- Motor neuron disease or related syndromes
  - Amyotrophic lateral sclerosis
  - Primary lateral sclerosis
  - Hereditary spastic paraplegia
- Inflammatory disorders
  - Multiple sclerosis
  - Systemic lupus erythematosus
  - Sarcoid
- Infectious diseases
  - HIV myelopathy
  - Bacterial disease
    - Syphilis
    - Tuberculosis (cord tuberculoma, compression)
  - Parasites
    - Schistosomiasis
    - Strongyloidosis
- Nutritional disorders
  - Combined systems disease (B_{12} deficiency)
  - Vitamin E (tocopherol) deficiency
  - Lathyrisin
- Neoplastic disease
  - Extramedullary (metastatic) or intramedullary tumors (primary or metastatic)
  - Paraneoplastic myelopathy
- Other disorders
  - Adrenoleukodystrophy
  - Hepatic myelopathy

Figure 12-95. Clinical manifestations of progressive multifocal leukoencephalopathy (PML). PML is caused by the opportunistic JC papovavirus. Multiple areas of demyelination occur, leading to the accumulation of different focal deficits (multifocal). When the lesions become extensive throughout the white matter, mental status changes ensue. PML occurs in immunosuppressed individuals. Before the AIDS epidemic, it was seen most often in those treated for lymphoproliferative disease (leukemia/lymphoma). PML is much more common in AIDS patients with a prevalence of about 2.5%. Recently, PML was reported in two multiple sclerosis patients enrolled in a clinical trial who received combination therapy of natalizumab and interferon-β-1a [70]. The disease progresses to death in months. There is no specific treatment.

Clinical Manifestations of Progressive Multifocal Leukoencephalopathy

- Multifocal symptoms and signs
  - Hemiparesis
  - Hemianopsia
  - Hemisensory deficit
  - Aphasia
  - Limb ataxia
  - Gait ataxia
  - Dysarthria
- Late mental status changes
  - Personality changes
  - Dementia

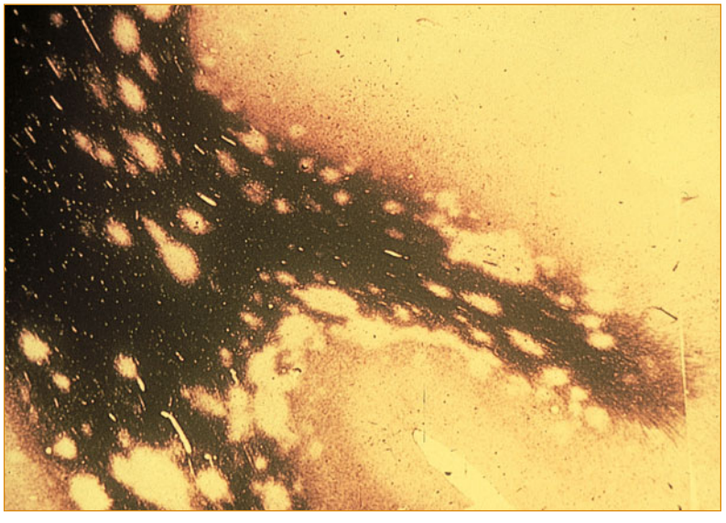


Figure 12-96. Photomicrograph showing the multiple pale areas of demyelination that are usually well-circumscribed in progressive multifocal leukoencephalopathy. These areas contain macrophages and virally infected astrocytes and oligodendroglia (lower power, myelin stain). The opportunistic JC papovavirus infects oligodendroglia of immunocompromised patients. This results in multiple areas of demyelination, which are greater in the cerebral white matter than the brain stem and cerebellum. Hyperplasia of astrocytes also occurs, and eosinophilic intranuclear inclusions are visible in enlarged oligodendroglia nuclei. (*Courtesy of* Richard Johnson, MD, Johns Hopkins Medical School, Baltimore, MD.)

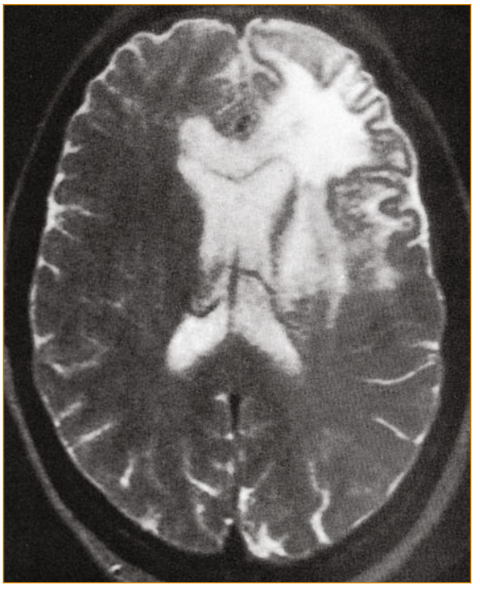


Figure 12-97. Diagnosis of progressive multifocal leukoencephalopathy (PML). T2-weighted axial MRI scan, with increased signal intensity in the left frontal lobe and corona radiata with extension across the midline in a patient with PML. As is characteristic, the subcortical U-fibers are involved. No specific findings occur in the cerebrospinal fluid (CSF), which is usually normal. The electroencephalographic changes are nonspecific. Serologic testing is not helpful, as most adults already have antibody to JC virus. Polymerase chain reaction amplification of JC viral DNA from the CSF is positive in about 80% of patients with PML. CT scans reveal low-density nonenhancing lesions without mass effect. MRI scans reveal increased signal intensity of T2-weighted, FLAIR, or diffusion-weighted images; enhancement is minimal in 10% to 15% of cases. Biopsy of the brain may be necessary for a definitive diagnosis. (*From* Whiteman *et al*. [71]; with permission.)

Subacute Sclerosing Panencephalitis

Clinical Stages of Subacute Sclerosing Panencephalitis (SSPE)

Stage I: Cerebral signs (mental, behavioral)	**Stage III: Coma, opisthotonus**
Irritability	No responsiveness to any stimulus
Affectionate displays	Extensor hypertonus
Lethargy	Decerebrate rigidity
Forgetfulness	Irregular, stertorous respiration
Indifference	**Stage IV: Mutism, loss of cerebral cortex function, myoclonus**
Withdrawal	Pathologic laughter, crying
Drooling	Wandering of eyes
Regressive speech	Flexion of upper and lower limbs
Slurred speech	Hypotonia
Stage II: Convulsive, motor signs	Turning of head to one side
Myoclonus of head, limbs, trunk	Occasional limb myoclonus
Incoordination of trunk, limbs	Startling by noise
Dyskinesia—choreoathetoid postures, movements, tremors	

Figure 12-98. Clinical stages of subacute sclerosing panencephalitis (SSPE). SSPE has become a rare disease in the United States, with fewer than 10 cases per year, since the introduction of measles vaccine. Most patients had their measles infection prior to the age of 2 years, followed by a latent period before the onset of disease, which occurs between the ages of 5 to 15 years in 85% of patients. The disease usually begins with poor school performance, personality changes and then dementia (forgetfulness, regressive speech), which is referred to as stage I. Myoclonus, seizures, and movement disorders occur in stage II. Eventually the comatose and akinetic mutism stages ensue. Death usually occurs in 1 to 3 years, but has ranged from several months to 15 years.

SSPE apparently is caused by the lack of production of the measles virus M protein, which is needed by the virus to bud out of the cell and spread efficiently to the next cell. This results in a cell-associated infection. The measles virus can spread only by cell fusion, which is slow and inefficient. Diagnosis is made from clinical manifestations and the characteristic laboratory abnormalities. One of the most characteristic laboratory tests is the electroencephalogram, which reveals periodic patterns of bursts occurring every 5 to 7 seconds followed by periods of background attenuation (burst-suppression). The cerebrospinal fluid gamma globulin and measles antibody titers are usually elevated. CT and MRI performed late in the course reveal diffuse atrophy of the cortex and white matter, with ex vacuo ventricular enlargement. MRI usually reveals multifocal gray and white matter lesions. Although there is no specific treatment, intrathecal administration of interferon-α with oral inosiplex has resulted in remissions. SSPE can be prevented with measles vaccination [72]. (*Adapted from* Ohya *et al*. [73].)

The Prion Diseases

Figure 12-99. Prion diseases of humans and animals. The prion diseases have also been referred to as transmissible spongiform encephalopathy agents. The first of these diseases, scrapie, was recognized to be transmissible in sheep in the 1930s. The latest epidemic of bovine spongiform encephalopathy in Britain, referred to by the lay public as "mad cow disease," is believed to have been transmitted to humans via the ingestion of contaminated beef resulting in a progressive dementia that has been named *new variant Creutzfeldt-Jakob disease* (nvCJD). The disease caused by nvCJD occurs in younger people and disease progression is slower [74]. Kuru is of historical interest because it was the first human prion disease to be recognized as transmissible. It occurs in the Fore Indians of New Guinea beginning with gait, trunk, and limb ataxia and involuntary movements (myoclonus, chorea, tremor) followed by dementia at a later date. Because it is transmitted primarily through cannibalistic rituals, which are now restricted, kuru is rare.

Prion Diseases of Humans and Animals

Disease	Host
Scrapie	Sheep, goats
Transmissible mink encephalopathy	Mink
Chronic wasting disease	Mule deer, elk
Bovine spongiform encephalopathy	Cattle
Feline spongiform encephalopathy	Cats
Kuru	Humans
CDJ	Humans
nvCJD	Humans
Gerstmann-Sträussler syndrome	Humans
Fatal familial insomnia	Humans

Characteristics of Prion Diseases and Agents
Prolonged incubation period of months to years
Progressive course of weeks to months to death
No host immune response (except astrocytosis)
Pathologic lesions confined to the central nervous system
Similar histopathology
Nonspecific treatment
Causative agents (prions) have specific properties:
No detectable nucleic acid
Resistant to alcohol, formalin, heat, ultraviolet irradiation, nucleases*
Susceptible to proteolytic enzymes, denaturing agents, organic solvents†
Sterilized by:
Steam autoclaving 1 h at 132° C
Immersion in 1N NaOH for 1 h at room temperature

**Agents that hydrolyze or modify nucleic acids.*
†Agents that digest, denature, or modify proteins.

Figure 12-100. Characteristics of the prion diseases and agents. One of the important characteristics of these agents is that they do not contain detectable nucleic acids (DNA, RNA) but do contain a protein, the prion protein (PrP), that must be transmitted for disease to occur. This finding led to the "prion" terminology, which was derived from "protein" and "infectious." There is no specific treatment for the various prion diseases. However, the agent (prions) can be disinfected with various sterilization procedures.

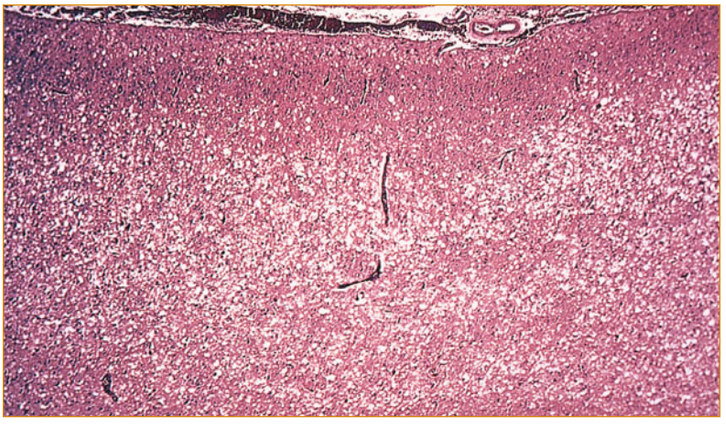


Figure 12-101. Low power view of hematoxylin-eosin stain showing spongiform change confined to the cerebral cortex with sparing of the white matter. Other gray matter areas such as the basal ganglia, thalamus, and cerebellum may also be involved. Spongiform change can also be due to the development of vacuoles in the neurons more than in the astrocytes. This would result in an overall loss of neurons. As previously noted, the prion protein (PrP) is associated with the transmission of disease. It is a hydrophobic protein with a molecular weight of 27 to 30 kD, referred to as PrP^{Sc} 27-30. Scrapie (Sc) is the prototype prion disease that has been analyzed in these studies. PrP^{Sc} 27-30 is the protease-resistant component of a larger protein, PrP^{Sc} 33-35. Subsequently, it was found that uninfected brains also contained a similar protein, PrP^{C} 33-35, which in humans has its gene (*PRNP*) on the short arm of chromosome 20. PrP^{C} 33-35 is fully degraded but PrP^{Sc} 33-35 is only degraded to PrP^{Sc} 27-30, which collapses to produce amyloid deposition. On electron micrographs "prion rods" (or "scrapie-associated fibrils") may be seen. PrP^{C} is found on the cell surface and has two transmembrane domains, while PrP^{Sc} accumulates within cells and extracellularly. The role of PrP^{C} is unknown. These findings have led to the hypothesis that in infected animals, PrP^{C} undergoes posttranslational modification being converted to the PrP^{Sc} isoform. This posttranslational modification would be the explanation for the sporadic prion diseases (Creutzfeldt-Jakob disease [CJD]). Prion disease can also be infectious (kuru, accidental CJD), or genetic (familial CJD, Gerstmann-Sträussler syndrome, fatal familial insomnia). Kuru is infectious and is transmitted most often during cannibalistic rituals. CJD has been transmitted by surgical instruments, stereotactic electroencephalogram needles, growth hormone preparations, dura matter grafts, and corneal transplants. In the genetic cases there are mutations in the *PRNP* gene. How the agent actually replicates in the sporadic and infectious cases is unclear. Pathologic changes are similar in all prion diseases with varying degrees of each feature. These features include spongiform change, astrocytosis, and deposition of amyloid or kuru plaques. (*From* Hirano *et al*. [41]; with permission.)

Clinical Characteristics of 232 Experimentally Transmitted Cases of Sporadic Creutzfeldt-Jakob Disease

	Patients with Symptoms or Signs, %		
Symptoms/Signs	**At Onset**	**On First Exam**	**During Course**
Mental deterioration	69	85	100
Memory loss	48	66	100
Behavioral abnormalities	29	40	57
Higher cortical functions	16	36	73
Cerebellar	33	56	71
Visual/oculomotor	19	32	42
Vertigo/dizziness	13	15	19
Headache	11	11	18
Sensory	6	7	11
Involuntary movements	4	18	91
Myoclonus	1	9	78
Other (including tremor)	3	12	36
Pyramidal	2	15	62
Extrapyramidal	0.5	9	56
Lower motor neuron	0.5	3	12
Seizures	0	2	19
Pseudobulbar	0.5	1	7
Periodic electroencephalogram*	0	0	60
Triphasic 1 cycle/sec	0	0	48
Burst suppression	0	0	14

**The figures shown are much lower than those published in a small series of repeatedly studied patients.*

Figure 12-102. Clinical and epidemiologic features of Creutzfeldt-Jakob disease (CJD). Usually there is a gradual onset of dementia in middle or late life. Prodromal symptoms may include anxiety, dizziness, blurred vision, unusual behavior, poor judgment, and fatigue. In addition to dementia, cerebellar signs often occur early and involuntary movements (especially myoclonus) and corticospinal tract and extrapyramidal signs eventually become prominent. So-called variant types, for example, lower motor neuron type and occipital type, have been categorized when these features are prominent early in the course. The incidence of CJD is 1 case per 1 million people per year and is the same throughout the world except for a few areas of high incidence (Libya, North Africa, Slovakia). CJD is not contagious but is transmissible, and general trauma, head and neck trauma, and head and neck surgery predispose a patient to the disease. Five percent to 15% of cases are familial, with an autosomal dominant pattern of inheritance. Mutations have been found in the *PRNP* gene in some of these familial cases and most often occur at codons 178 and 200. In a recent series the range for the age of onset was 16 to 82 years but only one patient was younger than 30 years old and four were younger than 40 years old. The mean duration of disease was 8 months; 80% to 90% die in 1 year. As previously noted, CJD is not contagious but the mode of transmission is unknown. The agent is not found in saliva or stool and only very rarely in urine. Therefore, it does not seem necessary to isolate patients. Because the agent is present in internal organs, blood and cerebrospinal fluid serum hepatitis precautions should be taken. (*Adapted from* Brown *et al*. [75].)

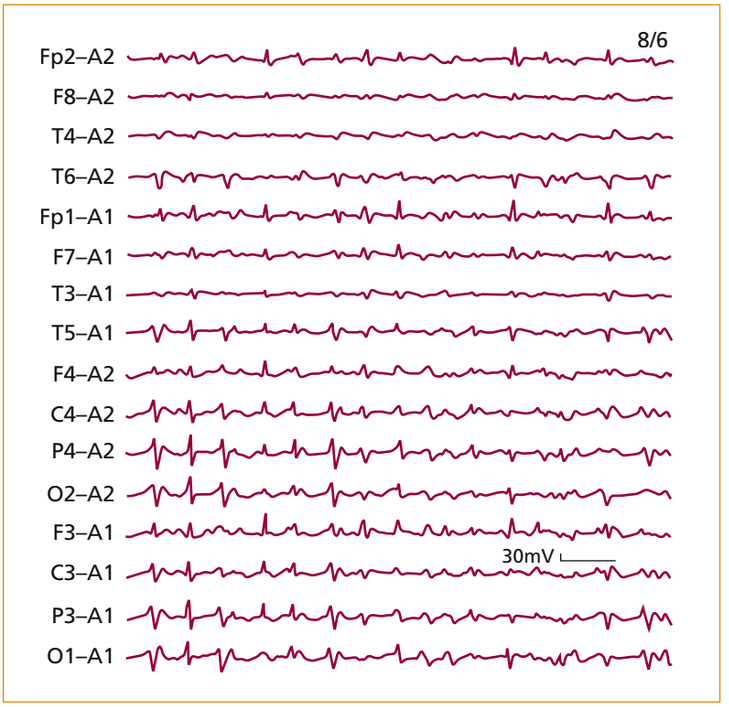


Figure 12-103. Diagnostic studies and diagnosis of Creutzfeldt-Jakob disease (CJD). Routine blood studies are normal. The cerebrospinal fluid (CSF) is also usually normal although the protein may be increased. Two dimensional isoelectric focusing of CSF proteins have revealed two abnormal protein species, now referred to as 14-3-3 neuronal proteins. The assay is positive in about 85% of sporadic CJD CSF samples. The assay may also be positive in other diseases with acute massive neuronal destruction such as herpes simplex encephalitis and acute infarction. MRI may be of equal sensitivity to the 14-3-3 assay for diagnostic purposes (*see* Fig. 12-104). The electroencephalogram (EEG) is the diagnostic test of choice. Various series report 60% to 95% of patients will have periodic complexes occurring on the average of one per second (range 0.5 to 2.5 seconds). Serial EEG may be needed to detect the periodicity, as it is usually absent at onset and early in the course and may also be absent late in the course. Diagnosis can also be made from brain biopsy but usually is not required. This electroencephalogram from a 65-year-old man with CJD shows periodic spikes or sharp waves every 0.7 seconds. (*Adapted from* Jubelt [76].)

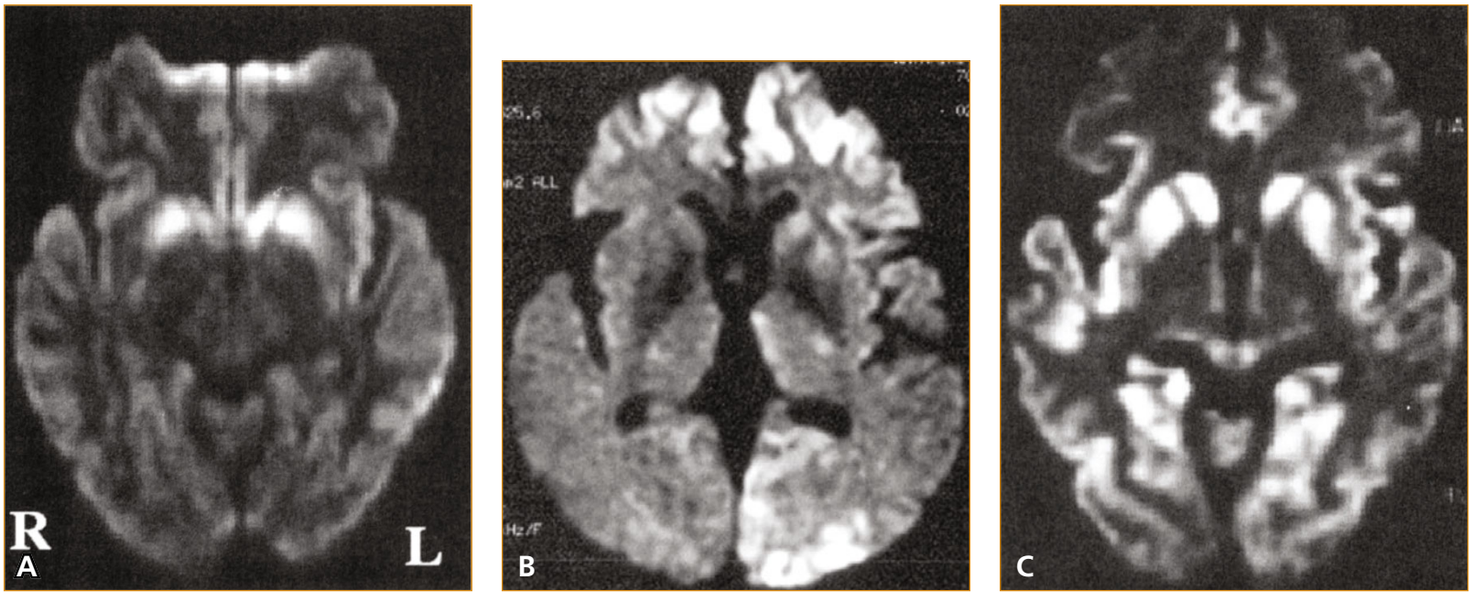


Figure 12-104. MRI of Creutzfeldt-Jakob disease. Increased signal intensity may be seen on T2-weighted, FLAIR, and diffusion-weighted imaging (DWI). Two patterns may be seen. The first is a diffuse pattern primarily seen in the basal ganglia and occasionally in the thalamus. The second is a cortical ribbon or gyriform pattern in the cortex and cerebellum. DWI appears to be more sensitive than either FLAIR or T2 imaging, with 90% to 100% sensitivity compared with about 50%. Three patterns of high intensity lesions were seen on DWI: striatal lesions (**A**), cerebral cortical lesions (**B**), and a combination of both lesions (**C**). (*From* Shiga *et al*. [77], with permission.)

Clinical Features of Variant Creutzfeldt-Jakob Disease

	Patients with Symptoms or Signs, % (n = 35)	
Symptoms/Signs	**At Onset**	**During Course**
Psychiatric	63	97
Sensory symptoms	20	68
Limb pain	11	37
Ataxia	8	100
Forgetfulness	17	83
Involuntary movements	6	94
Dystonia	6	34
Chorea	0	57
Myoclonus	0	71
Upgaze paresis	0	40
Dementia	0	100
Akinetic	0	57

Figure 12-105. Clinical features of variant Creutzfeldt-Jakob disease (vCJD). vCJD occurs at a younger age than classic CJD, with 89% dying before the age of 40. The duration of vCJD is also longer, with a median duration of illness of 14 months as compared to 9 to 11 months for classic CJD. vCJD usually begins with psychiatric symptoms and painful sensory symptoms rather than memory loss. Similar to classic CJD, dementia, ataxia, and involuntary movements eventually occur (*see* Fig. 12-102). Another unusual feature of vCJD is that the typical periodic triphasic complexes seen on electroencephalograms from classic CJD patients has not been reported. MRI may reveal abnormalities in the thalamus, but this finding is not specific for vCJD. (*Adapted from* Will *et al*. [78].)

Gerstmann-Sträussler-Schenker Syndrome

Characteristics of Gerstmann-Sträussler-Schenker Syndrome

- Familial autosomal dominant disease—*PRNP* gene mutations, most frequently at codons 102, 117, 198
- Age of onset—midlife
- Clinical signs
  - Early—cerebellar ataxia with gait ataxia
  - Later—limb ataxia, dysarthria, nystagmus, dementia, parkinsonism, deafness, blindness, gaze palsies
  - Eventually—corticospinal tract signs
- Course—lengthy, 2 to 10 years
- Treatment—supportive

Figure 12-106. Characteristics of Gerstmann-Sträussler-Schenker syndrome (GSS). GSS is an autosomal dominant familial disease. Clinically, patients appear to have spinocerebellar degeneration or olivopontocerebellar degeneration with cerebellar ataxia, which is the first most severe manifestation of the disease. Myoclonus is much less common. Eventually dementia and parkinsonism develop in most patients. The electroencephalogram does not usually show periodicity. In one reported case, early in the course, diffusion-weighted MRI revealed a cortical gyriform pattern in the frontal, temporal, and occipital cortices, followed by atrophy late in the course.

Fatal Familial Insomnia

Clinical Features of Fatal Familial Insomnia

Case	Sex	Age of onset, *y*	Course, *mo*	Insomnia	Dysautonomia	Ataxia	Myoclonus	Seizures	EEG
IV-20	F	48	7	+	+	+	+	–	–
IV-21*	M	52	9	+++[†]	+++	+	+	–	–
IV-34	F	45	7	+++	+(?)	+++	+	?	–
IV-37*	M	61	18	+++	+(?)	++	+	–	–
IV-75	M	54	18	++	++	++	+	–	–
IV-92	M	45	7	++	+++	?	+	–	+[§]
V-58*	F	35	25	+	+++	+++	+++	+[‡]	

**Clinically examined and longitudinally observed.*
[†]Polygraphically proven.
[‡]Grand mal type.
[§]Periodic spike activity.
+, minimal; ++, mild; +++, severe.

Figure 12-107. Clinical features of fatal familial insomnia (FFI). FFI is a rapidly progressive autosomal dominant disease of middle or late life. Mutation at codon 178 of the *PRNP* gene has been demonstrated. This change is similar to that reported for some cases of familial Creutzfeldt-Jakob disease, but the clinical picture is much different. FFI is characterized primarily by insomnia, dysautonomia, and ataxia. Dementia and a periodic electroencephalogram (EEG) are uncommon. The course progresses to death in a half to 2 years. (*Adapted from* Manetto *et al*. [79].)

Fungal Infections

Spectrum of Involvement for Fungi That Can Infect the CNS

			Chief Pathologic Manifestations		
Organisms	**Incidence**	**Predilection to Involve the CNS***	**Meningitis**	**Abscess or Inflammatory Mass**	**Infarct**
Cryptococcus	Common	++++	++++	+	+
Coccidioides	Common	+++	++++	+	+
Candida	Common	++	++	++	—
Aspergillus	Occasional	++	+	+++	++++
Zygomycetes†	Occasional	++	+	+++	++++
Histoplasma	Occasional	+	+	+	+
Blastomyces	Occasional	+	+	+	—
Sporothrix	Occasional	+	+	—	—
Paracoccidioides	Rare	±	±	±	—
Dematiaceous fungi	Rare	+++	±	++++	—
Pseudallescheria	Rare	+	++	++	—

** Versus other body sites.*
† The class of Zygomycetes or Phycomycetes includes genera Rhizopus and Mucor.
++++, common; ±, rare; —does not occur.

Figure 12-108. Clinical syndromes and frequencies of fungal infections that can affect the central nervous system (CNS). The clinical syndromes caused by fungi invading the CNS can be divided into meningitis, abscess or inflammatory mass (granuloma formations), and arterial thrombosis causing infarction. Fungi exist in two forms: yeasts and molds. Yeasts are unicellular organisms that have a thick cell wall surrounded by a well-defined capsule (*see* Fig. 12-112). Molds are composed of tubular filaments that sometimes have a branched form (hyphae). In the brain, dimorphic and fungal yeasts are more likely to cause meningitis, while molds are more likely to cause vasculitis with subsequent thrombosis and infarction. The major pathogenic molds are species of the genus *Aspergillus* and the class of Zygomycetes. (*Adapted from* Perfect [80].)

Factors Predisposing to Fungal CNS Infections

Predisposing Factors	**Typical Organisms**
Prematurity	*Candida*
Inherited immune defects CGD, SCID, etc.	*Candida, Cryptococcus, Aspergillus*
Acquired immune defects	
Corticosteroids	*Cryptococcus, Candida*
Cytotoxic agents	*Aspergillus, Candida*
HIV infection	*Cryptococcus, Histoplasma*
Alcoholism	*Sporothrix*
Hematologic malignancies	*Candida, Aspergillus, Cryptococcus, Histoplasma*
Iron chelator therapy	Zygomycetes
Deferoxamine	
Intravenous drug abuse	Zygomycetes, *Candida*
Diabetic ketoacidosis	Zygomycetes, *Candida*
Trauma, surgery, foreign body, near-drowning	*Candida, Pseudallescheria*, dematiaceous fungi

Figure 12-109. Predisposing factors to fungal infections of the central nervous system (CNS). As previously noted, most fungal infections are opportunistic. Specific factors predispose to specific fungal infections. CGD—chronic granulomatous disease; SCID—severe combined immune deficiency. (*Adapted from* Tunkel and Crous [81] and Gozdasoglu *et al*. [82].)

Fungal Meningitis

Signs and Symptoms of Fungal Meningitis

Fungal Organism	Fever (> 101° F)	Headache	Stiff Neck	Change in Mentation	Focal Signs	Visual Disturbance
Blastomyces	+	+++	+++	+	++	+
Candida	+++	+++	++	+	+	+
Coccidioides	+	+++	+	++	++	++
Cryptococcus	+	+++	+++	+	+	+++
Histoplasma	++	+	++	+	+	+
Sporothrix	+	++	++	++	+	?

+, rare; ++, occasionally to moderately frequently; +++, usually.

Figure 12-110. Signs and symptoms of fungal meningitis. The symptoms and signs of fungal meningitis, one of the many causes of chronic meningitis, vary somewhat depending on the specific organism. (*Adapted from* Tucker and Ellner [83].)

Cryptococcal Meningitis

A Clinical Presentation in Non-AIDS and AIDS Patients

Clinical Presentation	Non-AIDS, %	AIDS, %
Headache	87	81
Fever	60	88
Nausea, vomiting, malaise	53	38
Mental status changes	52	19
Meningeal signs	50	31
Visual changes, photophobia	33	19
Seizures	15	8
No symptoms or signs	10	12

B Laboratory Studies in Non-AIDS and AIDS Patients

Laboratory Findings	Non-AIDS, %	AIDS, %
Positive blood culture	—	30–63
Positive serum cryptococcal antigen	66	99
CSF opening pressure > 200 mm H_2O	72	62
CSF glucose < 2.2 mmol/L (40 mg/dL)	73	33
CSF protein > 0.45 g/L (45 mg/dL)	89	58
CSF leukocytes > 20 × 10^6/L	70	23
Positive CSF India ink preparation	60	74
Positive CSF culture	96	95
Positive CSF cryptococcal antigen	86	91–100

Figure 12-111. Clinical presentations (**A**) and laboratory studies (**B**) of cryptococcal meningitis. *Cryptococcus* is the most frequent cause of fungal meningitis in both non-AIDS and AIDS patients. It is a chronic meningitis, but in AIDS patients it may progress even more slowly and present only with fever and headache instead of the usual manifestations of meningeal signs, mental status changes, and cranial nerve palsies.

The usual cerebrospinal fluid (CSF) profile in cryptococcal meningitis, as well as most causes of fungal meningitis, is that of mononuclear (lymphocytic) pleocytosis, a low glucose level, and an elevated protein level. AIDS patients, however, often do not fit this typical CSF picture. Most striking is the fact that 65% of AIDS patients have a normal CSF cell count of fewer than 5 cells/mm^3. Diagnosis is confirmed by positive CSF culture result or a positive CSF cryptococcal antigen test. Polymerase chain reaction techniques are in development but appear to be more sensitive than culture. (*Adapted from* Tunkel and Scheld [84].)

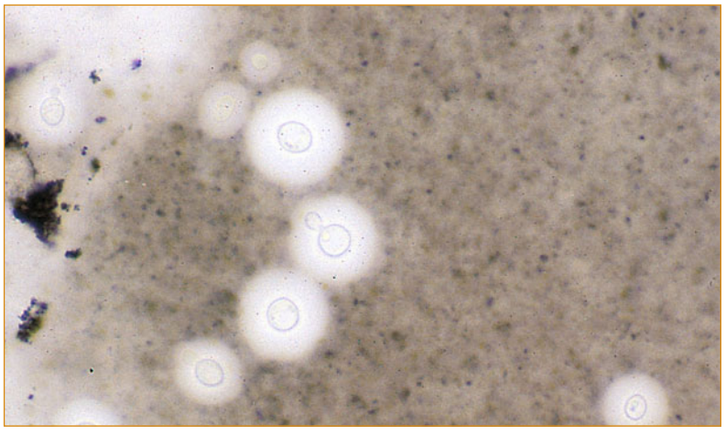


Figure 12-112. An India ink preparation used in the diagnosis of cryptococcal meningitis that demonstrates the prominent capsule of *Cryptococcus neoformans*. The India ink test is positive 50% to 60% of the time, and slightly more frequently in patients with AIDS (*see* Fig. 12-111**B**). (*From* Tunkel and Crous [81]; with permission.)

Coccidioidal Meningitis

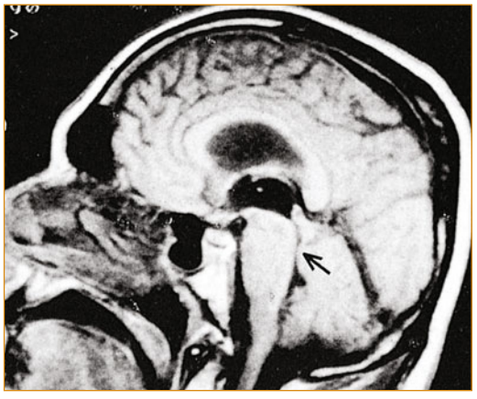


Figure 12-113. Magnetic resonance image showing enlargement of the third ventricle and the patent aqueduct (*arrow*), which are consistent findings with a communicating hydrocephalus. The diagnosis of coccidioidal meningitis depends on the recognition of the clinical picture of fungal meningitis and the extraneural manifestations of pulmonary and skin involvement. Unlike other fungal infections, about 70% of patients have a cerebrospinal fluid (CSF) eosinophilia. Positive CSF culture and antibody assays are required as the definitive criteria. Polymerase chain reaction techniques are under development. Hydrocephalus is a common complication of coccidioidal meningitis and may be communicating or noncommunicating. Patients with hydrocephalus have the highest mortality rates.

The clinical features of "cocci" meningitis are similar to those of cryptococcal meningitis except that changes in the patient's mental state are more likely to occur because of the earlier development of hydrocephalus. Other manifestations include fever, headache, and meningismus. *Coccidioides* is a common cause of fungal meningitis in areas where it is endemic. Fortunately, it is endemic only in the San Joaquin Valley and the desert areas of Central California. (*From* Galgiani [85]; with permission.)

Extraneural Manifestations of Fungi That Cause Meningitis

	Clinical Manifestations			
Species	**Respiratory Tract**	**Skin/Membranes**	**Hair**	**Bone/Joints**
Coccidioides	+++	++	—	+
Candida	+	+++	++	+
Histoplasma	++	+	—	—
Blastomyces	+++	+++	+	+
Sporothrix	+	++	—	++

+, low frequency; ++, moderate frequency; +++, high frequency.

Figure 12-114. Extraneural clinical manifestations of fungal meningitides. Unlike cryptococcosis, other fungi that cause meningitis have extraneural clinical manifestations that may be diagnostically valuable. These extraneural infections usually involve the respiratory tract, the skin, and hair. Clinical respiratory manifestations may be upper respiratory infection or pneumonia; the chest radiogram is often abnormal.

CSF Tests for Fungal Meningitis

Species	**Positive Culture Results**	**CSF Serologic Tests**
Blastomyces dermatitidis	Rare	Ab
Candida	50%	Ab/Ag
Coccidioides immitis	25%–45%	Ab
Cryptococcus neoformans	75%–80%	Ag
Dematiaceous fungi	Rare	None
Histoplasma capsulatum	50%	Ab
Paracoccidioides brasiliensis	Rare	Ab
Sporothrix schenckii	Rare	Ab

Figure 12-115. Cerebral spinal fluid (CSF) diagnostic tests for fungal meningitis. Other than extraneural manifestations, the main diagnostic studies are those performed on the CSF. Most patients with fungal meningitis have mononuclear pleocytosis, low glucose levels, and a high protein level similar to that seen in cryptococcal meningitis (*see* Fig. 12-111). Conclusive proof of diagnosis relies on culture and antigen (Ag) and antibody (Ab) tests. Unfortunately, CSF cultures often are not positive, but the likelihood of a positive result increases by culturing a large volume of CSF (15 to 30 mL). CT or MRI scans usually reveal at least some degree of hydrocephalus. Less frequently, single or multiple enhancing parenchymal lesions (abscesses) may be seen. (*Adapted from* Perfect [80].)

Differential Diagnosis of Fungal Meningitis Syndrome

Infectious	Noninfectious
Bacterial	Neoplasm
Tuberculosis	Sarcoidosis
Spirochetal (Lyme disease, syphilis, *Leptospira*)	Vasculitis
Agents that cause sinus tracts (*Actinomyces, Arachnia, Nocardia*)	Primary central nervous system angiitis
Brurcellosis	Systemic (giant cell arteritis, systemic lupus erythematosus, Sjögren's syndrome, rheumatoid arthritis, lymphomatoid granulomatosis, polyarteritis nodosa, Wegener's granulomatosis)
Listeria monocytogenes	Behçet's disease
Fungal	Chemical meningitis
Common (*Candida, Coccidioides, Cryptococcus, Histoplasma*)	Endogenous
Uncommon (*Aspergillus, Blastomyces,* dematiaceous fungi, *Paracoccidioides, Pseudallescheria, Sporothrix, Mucormycetes*)	Exogenous
	Intrathecal administration of systemic drugs
Parasitic	Chronic benign lymphocytic meningitis
Cysticercosis	Idiopathic hypertrophic pachymeningitis
Granulomatous amebic meningoencephalitis (acanthamoebiasis)	Vogt-Koyanagi-Harada disease
Eosinophilic meningitis (angiostrongyloidiasis)	
Toxoplasmosis	
Coenurus cerebralis	
Viral	
Retrovirus (HIV-1, human T-cell lymphotropic virus [HTLV-1])	
Enterovirus (in hypogammaglobulinemia)	
Parameningeal infections—epidural abscess, subdural empyema, brain abscess	

Figure 12-116. Differential diagnosis of fungal meningitis syndrome. Fungal meningitis is a subacute to chronic process with a course lasting over weeks to months, and the differential diagnosis of chronic meningitis is extensive. (*Adapted from* Hildebrand and Hildebrand [86].)

Primary Antifungal Therapy for Fungal Meningitides

Aspergillus	Voriconazole
Blastomyces dermatitidis	Amphotericin B then itraconazole
Candida	Amphotericin B plus 5-FC then fluconazole
Coccidioides immitis	Fluconazole then amphotericin B
Cryptococcus neoformans	Amphotericin B plus 5-FC then fluconazole
Histoplasma capsulatum	Amphotericin B then itraconazole
Sporothrix schenckii	Amphotericin B then itraconazole
Zygomycetes	Amphotericin B or liposomal amphotericin B

Figure 12-117. Treatment of fungal meningitis. Amphotericin B has been the main drug used for treatment of fungal meningitis for over 30 years. It remains the agent of choice alone or in combination with other treatment for most species. Amphotericin is primarily given intravenously, rarely intrathecally, for *Coccidioides*. For many species, this is followed with suppressive therapy with fluconazole or itraconazole. 5-FC—5-fluorocytosine. (*Adapted from* Perfect [80].)

Etiology of CNS Fungal Abscess

Species	Distribution of Cases %	Years of Survey	Species	Distribution of Cases,%	Years of Survey
Total cases, 39		1964–1973	Total cases, 61*		1956–1985
Candida	49		*Candida*	44	
Cryptococcus	23		*Aspergillus*	28	
Mucormycoses	13		*Cryptococcus*	23	
Aspergillus	5		Mucormycoses	3	
Histoplasmosis	5		Histoplasmosis	2	
Total cases, 11		1955–1971	Total cases, 57†		1984–1992
Aspergillus	64		*Aspergillus*		
Mucormycoses	27		*Candida*		
Candida	9		Mucormycoses		

**Includes meningitis plus abscess cases.*
†Bone marrow transplant recipients.

Figure 12-118. Etiology of fungal abscess of the central nervous system (CNS). Over the past 30 years fungal abscess has become more frequent due to the use of broad-spectrum antibiotics and immunosuppressive agents as well as the AIDS epidemic. Treatment may require agents to decrease intracranial pressure (mannitol, corticosteroids), surgical decompression, and antifungal chemotherapy agents (*see* Fig. 12-117). (*Adapted from* Sepkowitz and Armstrong [87].)

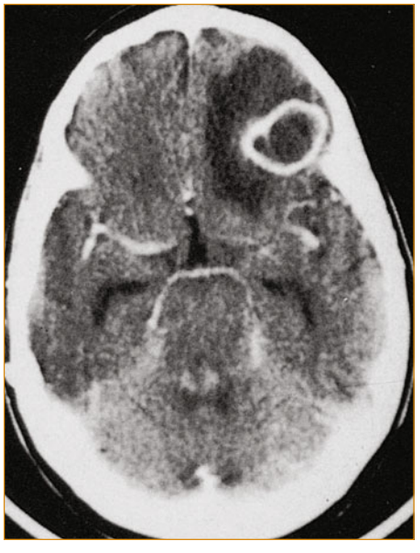


Figure 12-119. Contrast-enhanced CT scan that shows an aspergilloma in a 9-year-old boy with glioblastoma multiforme. For focal central nervous system fungal infections, CT and MRI are the diagnostic tests of choice. The cerebrospinal fluid analysis may be contraindicated because of increased intracranial pressure with a focal lesion. Culture specimens must be obtained at the time of surgical drainage and decompression. (*From* Sepkowitz and Armstrong [87]; with permission.)

Pathogenic Molds in the Central Nervous System

	Aspergillus Species	Mucorales	*Pseudallescheria boydii*
Patients at risk	Hematologic neoplasm	Diabetes with ketoacidosis (> 70%)	Near-drowning
	Neutropenia on broad-spectrum antibiotics	Hematologic neoplasm	Intravenous drug use
	Cortiocosteroids	Neutropenia on broad-spectrum antibiotics	Neutropenia on broad-spectrum antibiotics
	Organ transplants	Renal transplant	Hematologic malignancy
	Intravenous drug use	Intravenous drug use	Head trauma
	Liver disease	Deferoxamine therapy	
	Postcraniotomy	Acidosis	
	Subtropical farming		
Pathogenesis	Hematogenous	Rhinocerebral	Hematogenous
	Direct extension, including rhinocerebral (rare)	Hematogenous	Direct extension
			Traumatic implantation
Microscopic appearance	Septate hyphae	Nonseptate hyphae	Narrow septate hyphae with rare branching
	Acute branching	Broad right-angle branching	Narrow septate hyphae with rare branching
Culture from CSF	Rare	Seldom	Occasional
Treatment	Surgery	Surgery	Surgery
	Amphotericin B	Amphotericin B	Voriconazole
	? ± Fluconazole		
	? Itraconazole		

Figure 12-120. Pathogenic molds in the central nervous system. Molds may cause disease by direct extension, including rhinocerebral disease, and by invading blood vessels causing infarctions. It is rarely possible to culture these organisms from the cerebrospinal fluid (CSF) sample, but CSF antigen and antibody assays are available for *Aspergillus* as is a CSF antibody assay for Zygomycetes genera (*Mucorales* or *Mucor*). There are no CSF antigen or antibody tests for *Pseudallescheria boydii*. Aggressive treatment with surgery to remove necrotic tissue and antifungal chemotherapy are needed to cure these infections. (*Adapted from* Sepkowitz and Armstrong [87].)

Spirochete Infections

Neurosyphilis

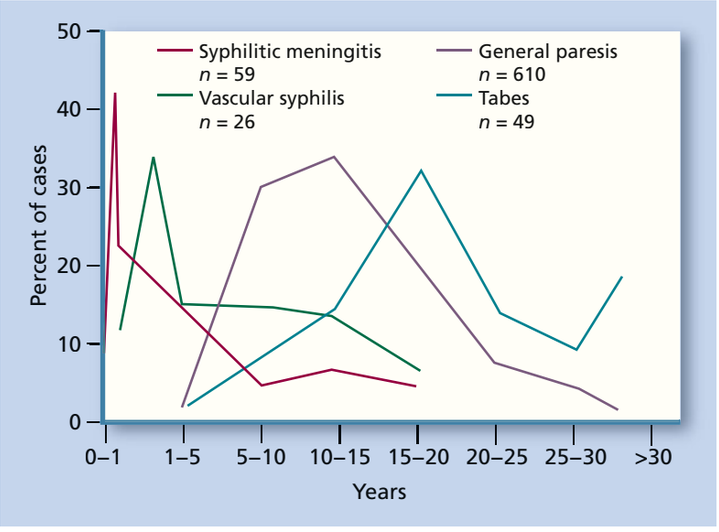


Figure 12-121. Time course for the appearance of neurosyphilic manifestations. Starting with the onset of the primary syphilitic infection of skin chancre, usually on the penis or perineum, the development of neurosyphilic syndromes over three decades is shown. Syphilitic meningitis occurs with either secondary or tertiary syphilis. All other syndromes of neurosyphilis occur during the tertiary stage. All forms of syphilis of the central nervous system ultimately result from active meningeal inflammation. When the meningeal inflammation extends to the cerebral blood vessels, cerebrovascular neurosyphilis results, usually within 5 years after the primary infection. The parenchymal forms of neurosyphilis—general paresis (dementia) and tabes dorsalis—occur after 5 years. Although each syndrome has a predictable time course, appearances often overlap and several syndromes may occur at the same time. (*Adapted from* Simon [88].)

Classification of Neurosyphilis

Type	Clinical Symptoms	Pathologic	CSF Leukocyte, *cells/mm*^{3}	Brain CT or MRI
Asymptomatic	No symptoms; CSF abnormal	Various. Chiefly leptomeningitis; arteritis or encephalitis may be present	< 5	Normal
			> 5	Meningeal enhancement
Meningeal and vascular				
Cerebral meningeal				
Diffuse (syphilitic meningitis)	Increased intracranial pressure; cranial nerve palsies	Leptomeningitis with hydrocephalus; degeneration of cranial nerves; arteritis	5 or more	Meningeal enhancement
Focal (gumma)	Increased intracranial pressure; focal cerebral symptoms and signs of slow onset	Granuloma formation (gumma)	Any	Mass lesion
Cerebrovascular	Focal cerebral symptoms and signs of sudden onset	Endarteritis with infarcts	Any	Subcortical or cortical intact
Spinal meningeal and vascular	Paresthesia, weakness, atrophy, and sensory loss in limbs and trunk	Admixture of endarteritis and meningeal infiltration and thickening with degeneration of nerve roots and substance of the cord—myelomalacia	Any	NA
Parenchymatous				
Tabetic	Pain, paresthesia, crises, ataxia, impairment of pupillary reflexes, loss of tendon reflexes, impaired proprioceptive sensation, and trophic changes	Leptomeningitis and degenerative changes in posterior roots, dorsal funiculi, and brain stem	Any	NA
Paretic	Personality changes, convulsions, and dementia	Meningoencephalitis	Any	Optic atrophy
Optic atrophy	Loss of vision, pallor of optic discs	Leptomeningitis and atrophy of optic nerves	Any	NA

Figure 12-122. Classification of neurosyphilis. Neurosyphilis encompasses several different syndromes because the causative organism, *Treponema pallidum*, is able to infect the meninges, the blood vessels, and the brain and spinal cord parenchyma. Asymptomatic neurosyphilis is diagnosed by positive serologic findings in both the blood and the cerebrospinal fluid (CSF). CSF pleocytosis with mononuclear cells could allow diagnosis of asymptomatic syphilitic meningitis. NA—not applicable. (*Adapted from* Stefanis and Rowland [89].)

Cranial Nerve Palsies in Syphilitic Meningitis*

Cranial Nerves	Percent of Abnormalities
I	2
II	27
III	24
IV	2
V	12
VI	22
VII	41
VIII	42
IX–X	6
XI	1
XII	4

**354 cranial nerve palsies in 195 patients.*

Figure 12-123. Cranial nerve palsies in syphilitic meningitis. Symptomatic meningeal syphilis usually occurs during the first 2 years after the primary infection. In approximately 10% of cases, syphilitic meningitis occurs with the rash of secondary syphilis, but most cases occur during the tertiary stage. Patients present with headache, meningismus, and malaise. They may or may not have a low-grade fever. Lymphocytic pleocytosis of up to several hundred cells occurs; the cerebrospinal fluid (CSF) glucose level is reduced, but usually is greater than 25 mg/dL; CSF protein level is increased and may exceed 100 mg/dL; and the CSF pressure may be elevated. This syndrome is diagnosed with positive blood and CSF serologic tests (serologic tests for syphilis: Venereal Disease Research Laboratories, rapid plasma reagin). The syndrome may resolve on its own, or complications may ensue. Because the meningitis is most concentrated at the base, cranial nerve palsies are often seen, sometimes bilaterally but usually asymmetrically. Obstruction of CSF pathways may result in subacute to chronic hydrocephalus. (*Adapted from* Merrit *et al*. [90].)

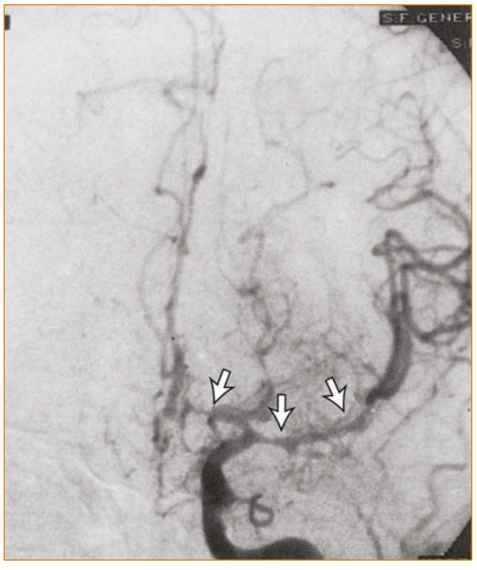


Figure 12-124. Anteroposterior view, left carotid angiogram, of a 26-year-old man with meningovascular syphilis, showing constriction (*arrows*) of the anterior and middle segments of the middle cerebral artery. Cerebrovascular syphilis occurs when the inflammation in the subarachnoid space compromises arteries traversing this space. Vasculitis of middle-sized vessels occurs, resulting in ischemia. The middle cerebral artery is affected most often, but any cerebral or spinal vessel may be involved. Stroke syndromes occurring in neurosyphilis are no different than those seen from other causes; focal clinical manifestations are determined by which vessel is involved. The patients exhibit risk factors for venereal disease and are usually younger than those with arthrosclerotic infarction. Differentiation depends upon the blood and cerebrospinal fluid serologic results. CT or MRI scans of the brain reveal cortical or subcortical infarction. If the meningeal inflammation is intense enough, a prodrome of headache and personality change may precede the stroke by weeks (meningovascular syphilis). Penicillin effectively cures the infection, preventing further infarctions. (*From* Simon and Bayne [91]; with permission.)

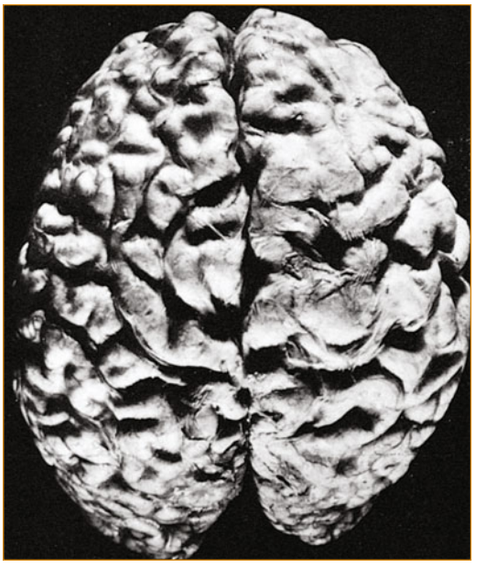


Figure 12-125. Pathologic specimen from a brain with paretic neurosyphilis. Paretic neurosyphilis has also been referred to as general paresis of the insane, syphilitic meningoencephalitis, dementia paralytica, and syphilitic dementia. Symptoms usually begin 5 to 15 years after the primary infection, with a range of 3 to 30 years. Paretic neurosyphilis was common in the preantibiotic era but is now infrequent. The symptoms and signs of general paresis are similar to any organic brain syndrome. Progressive dementia with personality changes is the most common feature. Behavioral changes with psychosis and grandiose delusional states are unusual. Seizures also are seen. Masked facies; tremors of the face, tongue, lips, and extremities; dysarthria; and hyperactive reflexes may also occur. Pathologically there is chronic meningoencephalitis with cortical atrophy, enlarged ventricles, thickened meninges, and granular ependymitis. Microscopic lesions include mononuclear inflammatory cells, a prominent microglial rod cell response, and the presence of the organisms. Diagnosis depends on cerebrospinal fluid abnormalities and serologic results. Usually patients are younger (less than 50 years of age) than those with other causes of dementia. Penicillin is an effective therapy and usually arrests the progression of the dementia but will not reverse the existing damage. (*From* Merrit *et al*. [90]; with permission.)

A Symptoms and Signs of Tabetic Neurosyphilis (Analysis of 150 Cases)

Symptoms	%	Signs	%
Lancinating pain	75	Abnormal pupils	94
Ataxia	42	Argyll-Robertson	48
Bladder disturbance	33	Other abnormalities	46
Paresthesia	24	Absent reflexes	
Gastric or visceral crises	18	Ankle jerks	94
Optic atrophy	16	Knee jerks	81
Rectal incontinence	14	Biceps and triceps	11
Deafness	7	Romberg sign	55
Impotence	4	Impaired sensations	
		Vibratory sense	52
		Position sense	45
		Touch and pain	13
		Ocular palsy	10
		Charcot joints	7

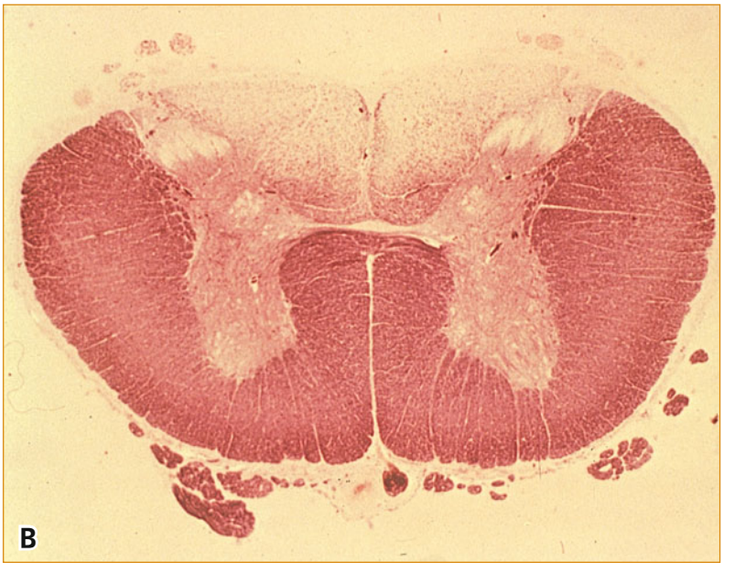


Figure 12-126. Symptoms and signs of tabetic neurosyphilis. Tabetic neurosyphilis is also referred to as tabes dorsalis because of the degeneration of the posterior columns. Tabes usually begins 10 to 20 years after the primary infection, but some cases have had onset after 30 years (range, 5–50 years). **A**, The most common and classic symptoms of tabes are the lancinating or lightning-like pains, ataxia, and bladder dysfunction. Prominent signs include abnormal pupils including Argyll-Robertson pupils, absent reflexes in the lower extremities, loss of posterior column sensations, Romberg sign, and gait ataxia. As the disease progresses, bladder dysfunction and the sensory gait ataxia usually become the most disabling problems. Loss of deep pain sensation may occur with Abadie's sign (loss or delayed recognition of pain when the Achilles tendon is squeezed). Charcot joints and distal extremity ulcerations may be seen. **B**, Pathologically, degeneration of the posterior columns and dorsal roots occurs. Diagnosis is relatively easy because of the classic clinical manifestations, with positive serologic results, at least in the blood samples. The disease may arrest spontaneously or may be arrested with antibiotic treatment. The latter is more likely to occur when there are signs of active inflammation in the cerebrospinal fluid (CSF). Even after treatment, and even when there is no active CSF inflammation (as regards CSF pleocytosis), many of the manifestations may continue to progress. The pathogenesis of tabes is not understood. In contrast to paretic cortical lesions, spirochetes are not found in the affected areas of the spinal cord, which may explain why antibiotic therapy may not stop progression. (**A**, *adapted from* Merrit *et al*. [90]; **B**, *from* Wilson [4]; with permission.)

Frequency of Different Forms of Symptomatic Neurosyphilis*

	Preantibiotic Era			Antibiotic Era		AIDS Era	
						HIV (-)	HIV (+) or AIDS
	1	2	3	4	5	6	7
Tabetic	45	48	45	15	11	5	0
Paretic	17	48	8	12	4	9	4
Taboparetic	4	7	9	23	23	—	—
Vascular	15	19	9	19	61	41	38
Meningeal	8	8	19	23	0	23	46
Optic neuritis	4	—	—	—	—	14	42
Spinal cord	4	—	10	8	—	—	—

** Numbers are a percentage of cases.*
1 Merritt, Adams, Solomon, 1946 (457 patients).
2 Kierland et al., 1942 (2019 patients).
3 Wolters, 1987 (518 patients, 1930–1940).
4 Wolters, 1987 (121 patients, 1970–1984).
5 Burke, Schaberg, 1985 (26 patients).
6, 7 Katz et al., 1993.

Figure 12-127. Frequency of different forms of symptomatic neurosyphilis. Following the introduction of penicillin, the frequency of neurosyphilis per hospital admission fell from 5.9 per 100,000 population in 1942 to 0.1 per 100,000 in 1965. Beginning in the 1980s and coincident with the AIDS epidemic, this trend has been reversed. The incidence of neurosyphilis is unknown, but the incidence of primary and secondary syphilis has risen from 13.7 per 100,000 population in 1981 to a peak of 20.1 per 100,000 in 1990. Since then the incidence has dropped significantly, perhaps because of better surveillance and education. The overall frequency of neurosyphilis in HIV-positive and AIDS patients is estimated to be 2%. Also during the 1980s and 1990s, a shift occurred toward meningeal and vascular forms of neurosyphilis and a decline in the parenchymal forms. This may be related to cerebrospinal fluid abnormalities of neurosyphilis in HIV-infected patients, which are more intense than those of non–HIV-infected patients. (*Adapted from* Stefanis and Rowland [89].)

CSF Findings in Neurosyphilis by Clinical Syndrome (Subtype)

Neurosyphilic Syndrome	OP mm H_2O	Leukocyte Level, *per mm³*	Glucose Level, *mg/dL*	Protein Level, *mg/dL*	VDRL Blood	VDRL CSF
Meningitic	210–400*	100–500†	20–40	45–200	1:64	1:4
	(< 200 to > 400)	(< 10–2000)	(< 20 to > 80)	(< 45–400)		
Cerebrovascular	< 200 (> 200–250)	10–100 (< 10 to > 100)	Normal to mildly decreased	100–200 (15–260)	1:512	1:16
Paretic	< 200 (< 200–300)	10–100 (< 10 to > 100)	Normal to mildly decreased	45–100 (29–500)	1:128	1:8
Tabetic	< 200	Active 5–50	Normal	45–100	Active 1:15	1:28
	(< 200–300)	(5–165)		(14–250)	Inactive 1:16	1:2
		Inactive 0–5				

** Numbers without parentheses are the common range. Numbers in parentheses are the overall range.*
† CSF pleocytosis is usually 80% to 100% lymphocytic mononuclear.

Figure 12-128. Abnormalities of cerebrospinal fluid (CSF) in neurosyphilis. The diagnosis of active neurosyphilis is based upon a compatible clinical syndrome, an inflammatory CSF profile, and reactive serologic tests in the blood (treponemal antibody test) and CSF (nontreponemal test). CSF pleocytosis (primarily lymphocytic) is the best measure of disease activity. The number of cells varies with each clinical subtype, being maximal in the earlier acute-like stage of syphilitic meningitis. The glucose level is usually low in syphilitic meningitis and is more likely to be normal for other subtypes. CSF protein levels are usually elevated for all subtypes. The CSF gamma globulin level may be increased and oligoclonal bands may be present. OP—opening pressure, VDRL—Venereal Disease Research Laboratory. (*Adapted from* Simon and Bayne [91].)

Serologic Tests Used in the Diagnosis of Neurosyphilis

Test	Abnormality Required for Diagnosis	False/Positive Tests
FTA-ABS or MHA-TP	+ in blood required	Rare
	- excludes diagnosis	Other spirochete diseases
		Autoimmune diseases, especially systemic lupus erythematosus (SLE)
VDRL	+ in CSF required for diagnosis	Contamination of CSF by blood
		CSF paraprotein
	- in CSF inactive or no neurosyphilis	Very high CSF protein level
		Autoimmune disease (such as SLE)
		Strong immunologic stimulus
		Acute bacterial or viral infections
		Early HIV infection
		Vaccination
		Central nervous system neoplasia
		Drug addiction
		Pregnancy
		Chronic liver disease

Figure 12-129. Serologic tests used in the diagnosis of neurosyphilis. Diagnosis of neurosyphilis depends on a compatible clinical syndrome, an inflammatory cerebrospinal fluid (CSF) profile, and reactive serologic tests. The treponemal antibody tests are the fluorescent treponemal antibody-absorption (FTA-ABS) test and the microhemagglutination test for *Treponema pallidum* (MHA-TP). Positive blood FTA-ABS and MHA-TP are diagnostic for syphilis, as they are highly specific and remain positive for years. If these tests are negative, the diagnosis of neurosyphilis is essentially excluded; they are not useful, however, for following disease activity because they do not revert with successful treatment. These treponemal antibody tests are not useful for CSF analysis. The serologic diagnosis of neurosyphilis requires a positive blood serologic result and a reactive CSF serologic test for syphilis (STS). The two STS tests used currently are the Venereal Disease Research Laboratory (VDRL) test and the rapid plasma reagin (RPR) test. The RPR test cannot be used on the CSF. The CSF VDRL test can be used to follow disease activity after treatment but is not as reliable as the CSF pleocytosis.

Figure 12-130. Treatment regimens for neurosyphilis. The cerebrospinal fluid (CSF) inflammatory process (increased cell count) is the best indicator of disease activity and should be monitored for successful treatment. Normalization of CSF pleocytosis and protein level is the ultimate goal of treatment. The CSF Venereal Disease Research Laboratory test titer should also be followed, but it is not as sensitive to treatment as the CSF pleocytosis. Penicillin remains the drug of choice with the regimens shown here. Benzathine penicillin G does not produce adequate levels in the CSF for treatment. After treatment, the clinical examination should stabilize and the blood serologic test levels should decline. The CSF is examined at 6 and 12 months after treatment. At 6 months, the cell count should be normal and protein level falling; by 12 months, both are usually normal. If cells are still present at 6 or 12 months, retreatment is required. If the protein level is still elevated at 12 months, the CSF should be reexamined in 2 years. Retreatment is required if there has been clinical progression or the CSF is still abnormal. The same treatment regimen is recommended for HIV-coinfected patients as for non-HIV patients. IM—intramuscular; IV—intravenous; po—per os (by mouth). (*Adapted from* Simon and Bayne [91].)

Treatment Regimens for Neurosyphilis

Established

Aqueous crystalline penicillin G, 12 to 24 million U IV daily (divided doses q4h) for 10–14d

Approved

Aqueous procaine penicillin G, 2.4 million U IM daily, plus probenecid 500 mg po qid for 10–14 d

Under study

Ceftriaxone 1 g IV q12h

Alternate drug regimens for penicillin-allergic patients

Desensitize to penicillin (preferred alternative)

Tetracycline hydrochloride 500 mg po qid for 30 d

Doxycycline 200 mg po bid for 21 d

Erythromycin 500 mg po qid for 30 d

Chloramphenicol 1 g IV qid for 14 d

Ceftriaxone 1 g q12h (under study)

Recommended treatment regimens for syphilis in HIV-coinfected patients

No change in therapy for early syphilis (CSF examination may be a useful guide to adequate treatment)

Benzathine penicillin should not be used

Examine CSF before and following treatment as a treatment guide

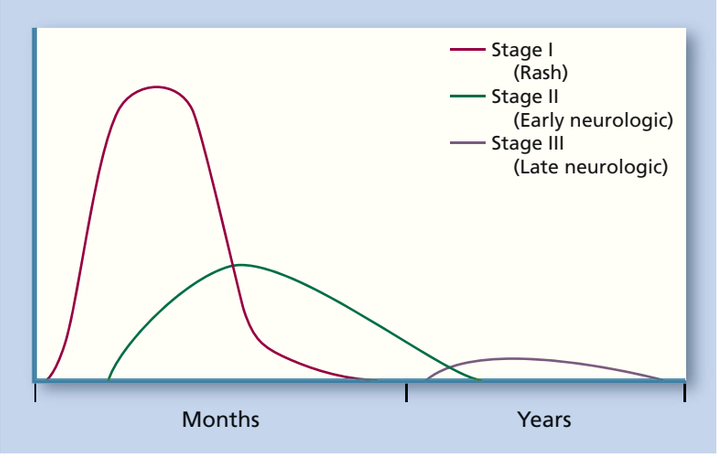
Aqueous crystalline penicillin G IV, 12–24 million U daily (2–4 million U q4h)

Aqueous or procaine penicillin G, 2.4 million U IM daily plus probenecid 500 mg po qid

Lyme Disease

Figure 12-131. Clinical stages of Lyme disease. Lyme disease results from infection by the spirochete *Borrelia burgdorferi*, which is transmitted by ticks. Lyme disease may develop into a chronic persistent infection in a fashion somewhat similar to syphilis. For this reason, Lyme disease has been divided into stages. The nervous system is involved clinically in 10% to 15% of patients. Stage I, the acute stage, is characterized by a rash—erythema chronicum migrans (ECM)—which is an erythematous ring that develops around the tick bite site about 8 to 9 (range 3 to 32) days after exposure. Smaller secondary (migratory) rings may occur later. Neurologic manifestations may occur in stage I concurrently with ECM, but they are more frequent in stage II. Stage II, the subacute stage, is characterized by prominent cardiac and neurologic manifestations. This stage usually begins several months after the bite and the onset of ECM. Stage III, the chronic stage, is characterized by chronic arthritis. Neurologic manifestations also occur in stage III but they are less prominent than those of stage II. Stage III usually begins about 1 year after onset.

In the acute stage I, a systemic flu-like syndrome with fever, chills, and malaise may occur. Neurologic manifestations include headache and neck stiffness but normal cerebrospinal fluid (CSF) parameters. Stage II is also referred to as the "early neurologic stage" because dissemination of the organism to the central nervous system begins. During this stage, aseptic meningitis with complications of cranial nerve palsies, especially facial (Bell's palsy), and radiculoneuritis are most prominent. The facial or Bell's palsy is usually bilateral. The radiculoneuritis may take the form of a Guillain-Barré–like syndrome, but the CSF shows pleocytosis; sometimes the radiculoneuritis is focal. Occasionally, mild meningoencephalitis along with irritability, emotional lability, decreased concentration and memory, and sleep abnormalities may occur.



Stage III or the chronic stage is also referred to as the "late neurologic stage." This stage is characterized by chronic or late persistent infection of the nervous system. Syndromes included in this stage are encephalopathy, encephalomyelopathy, and polyneuropathy. The encephalopathy is characterized by memory and other cognitive dysfunction. The encephalomyelopathic signs are combined with progressive long tract signs and optic nerve involvement. White matter lesions may be visible on MRI of the brain. The late polyneuropathy is primarily sensory. (*Adapted from* Davis [92].)

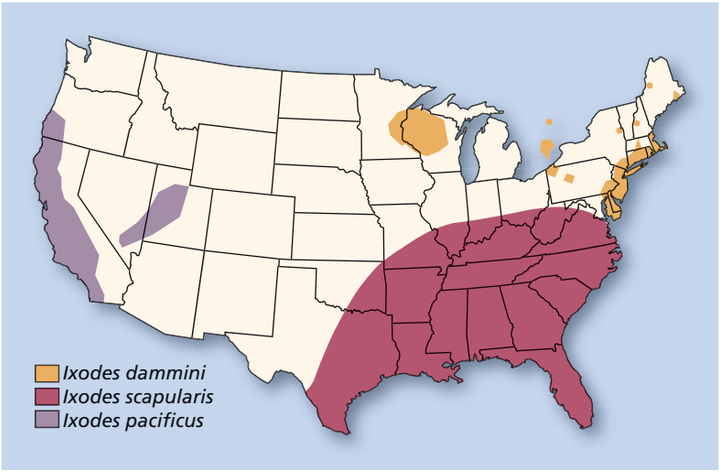


Figure 12-132. Epidemiology of Lyme disease. Lyme disease accounts for about 90% of the vector-borne infections in the United States. In 2005, over 23,000 cases were reported to the Centers for Disease Control and Prevention. *Borrelia burgdorferi*, the spirochete that causes Lyme disease, is transmitted by *Ixodes* species (hard body) ticks. Up to 50% of human infections are asymptomatic. The infection rate of different *Ixodes* species carrying the spirochete depends on the species. *Ixodes dammini* (deer tick) is the principal vector in the Northeast (30% to 60% infection rate) and the Midwest (10% to 15% infection rate). *Ixodes pacificus* (western black-legged tick) is the vector in the West (1% to 5% infection rate). In the southeastern United States, *Ixodes scapularis* is the vector but its infection rate is much lower even than that of *I. pacificus*. The various infection rates of the different *Ixodes* species explains why 10 states account for almost 90% of the cases: New York (40%), followed by Connecticut, New Jersey, Pennsylvania, Rhode Island, Massachusetts, Maryland, Wisconsin, Minnesota, and California. In the figure, the *circles* indicate collection sites outside the main range of *I. dammini*. (*Adapted from* Anderson [93].)

CSF Analysis in Lyme Disease Encephalomyelitis

Test	CSF Findings
Opening pressure*	Normal
Total leukocytes/mm^3	166 (15–700)†
Percent lymphocytes	93 (40–100)
Glucose, *mg/dL*‡	49 (33–61)
Protein, *mg/dL*	79 (8–400)
IgG/albumin ratio (*n* = 20)	0.18 (0.9–0.44)
Oligoclonal bands (*n* = 4)	Present
Myelin basic protein (*n* = 5)	Absent
VDRL (*n* = 20)	Negative

**n = 38, except where noted.*
†Median (range).
‡Serum glucose = 95 (87–113).

Figure 12-133. Cerebrospinal fluid (CSF) analysis in Lyme disease encephalomyelitis. CSF is usually abnormal in central nervous system Lyme disease and generally normal in peripheral nervous system syndromes unless there is radicular involvement. CSF analysis is usually abnormal and has a higher diagnostic yield than electroencephalography (usually normal or nonspecific) or MRI (25% have small cerebral white matter lesions). CSF analysis also offers the opportunity to test for the intrathecal production of *Borrelia burgdorferi* antibodies. VDRL—Venereal Disease Research Laboratory. (*Adapted from* Pachner and Steere [94].)

Causes of False-positive and False-negative Lyme Serologic Tests

False-positive
- Cross-reactive spirochetal infection (*eg*, mouth treponemes, syphilis, leptospirosis, relapsing fever)
- Severe bacterial infections
- Hypergammaglobulinemia
- Epstein-Barr virus
- Autoimmune disorders with high autoantibody titers
- HIV infection
- Unreliably easy

False-negative
- Too early in the infection
- Early antibiotics with blurred humoral response
- Unreliably easy

Figure 12-134. Causes of false-positive and false-negative Lyme disease serologic tests. Serum antibodies, when present, prove exposure to the agent but cannot be used to determine when the infection occurred. Most antibody assays are now performed by an enzyme-linked immunosorbent assay technique. Western blot testing is required to confirm the diagnosis. Polymerase chain reaction testing is still experimental. The demonstration of elevated *Borrelia burgdorferi* antibodies in the cerebrospinal fluid is essentially diagnostic. About 95% of Lyme disease patients are seropositive, but false-positive and false-negative test results may occur. (*Adapted from* Coyle [95].)

Neurologic Conditions in Which Lyme Disease Should Be Considered

Central Nervous System	Peripheral Nervous System
Acute aseptic meningitis	Cranial neuritis (Bell's palsy)
Chronic lymphocytic meningitis	Mononeuritis simplex or multiplex
Acute meningoencephalitis	Radiculoneuritis
Acute focal encephalitis	Plexitis
Brainstem encephalitis	Distal axonal neuropathy
Progressive encephalomyelitis	Demyelinating neuropathy
Cerebral demyelination, including multiple sclerosis	Carpal tunnel syndrome
Cerebral vasculitis	Focal myositis
Dementia	
Transverse myelitis	

Figure 12-135. Differential diagnosis of Lyme disease. The combination of meningitis, neuritis, and radiculitis without fever is highly suggestive of Lyme disease. If a history of tick exposure or erythema chronicum migrans is obtained, the diagnosis can be made with confidence. Because of the involvement of both the peripheral and the central nervous systems, the differential diagnosis is varied and extensive. (*Adapted from* Reik [96].)

Antibiotic Therapy for Neurologic Symptoms of Lyme Disease

Manifestations	Treatment
ECM and systemic symptoms	Doxycycline, 100 mg po bid for 14–28 d
Adults	Amoxicillin, 500 mg po tid for 14–28 d (plus probenecid, 500 mg po tid)*
	Cefuroxime axetil, 500 mg po bid for 14–28 d†
Children (≤ 8 y)	Amoxicillin, 25–50 mg/kg po daily in 3 divided doses for 14–28 d
	Cefuroxime axetil, 250 mg po bid for 14–28 d†
Neurologic involvement	
Facial palsy alone	Oral antibiotics as for ECM
All others	
Adults	Ceftriaxone, 2 g IV daily for 14–28 d
	Cefotaxime, 2 g IV tid for 14–28 d
	Penicillin G, 20–24 million U IV daily for 10–14 d
	Doxycycline, 200 mg po bid for 14–28 d
Children	Ceftriaxone, 75–100 mg/kg IV daily for 14–28 d
	Penicillin G, 300,000 U/kg IV q 4 h for 10–14 d

**Optional.*
†Alternative.

Figure 12-136. Antibiotic therapy for neurologic syndromes of Lyme disease. The antibiotic therapy for neurologic syndromes depends on the specific stage of Lyme disease. Ceftriaxone IV is now usually considered the drug of choice for stages II (early neurologic stage) or III (late neurologic stage). Most symptoms resolve with antibiotic treatment, but motor signs may last for 7 to 8 weeks. The duration of therapy has never been clarified. A postinfectious syndrome with symptoms of fatigue, headache, and muscle and joint pain may last for months to several years. ECM—erythema chronicum migrans; IV—intravenous; po—per os (by mouth). (*Adapted from* Cadavid [97].)

Parasitic Infections

Major Protozoan and Helminthic Infections of the Central Nervous System

- Protozoan
  - Toxoplasmosis
  - Cerebral malaria
  - Trypanosomiasis
  - Amebic meningoencephalitis
- Nematodes (roundworms)
  - Trichinosis
  - Eosinophilic meningoencephalitis
  - *Angiostrongylus cantonensis*
  - *Gnathostoma spinigerum*
  - Strongyloidiasis
  - Toxocariasis (visceral larva migrans)
  - Human filariases
  - Onchocerciasis (river blindness)
  - Dracunculiasis
- Trematodes (flukes)
  - Schistosomiasis
  - Paragonimiasis
- Cestodes (tapeworms)
  - Cysticercosis
  - Hydatid disease *(Echinococcus)*

Figure 12-137. Major protozoan and helminthic infections of the central nervous system. Toxoplasmosis is the most important protozoan infection in developed countries, where it occurs in immunosuppressed individuals. Worldwide malaria is the most important protozoan infection. Cysticercosis is probably the most important helminthic infection causing central nervous system disease. (*Adapted from* Coda [98].)

Protozoa

Protozoan Infections of the Nervous System

Disease/Parasite	Geographic Distribution	Risk Factor	Neurologic Disease
Toxoplasmosis			
Toxoplasma gondii	Worldwide	Perinatal infection, immunosuppression	Diffuse, focal, or multifocal encephalitis, chorioretinitis
Malaria			
Plasmodium falciparum	Tropics and subtropics	Mosquitoes	Acute encephalopathy
Trypanosomiasis			
African			
Trypanosoma gambiense	Tropical West African forest	Tsetse flies	Chronic encephalitis
Trypanosoma rhodesiense	East equatorial Africa		Subacute meningoencephalitis
South American			
Trypanosoma cruzi	Mexico to South American	Reduviid bugs	Acute meningoencephalitis (rare) Chronic parasympathetic denervation of gastrointestinal tract
Amebiasis			
Entamoeba histolytica	Worldwide	Poor water and sewage, institutionalized persons, homosexuals	Brain abscess (rare)
Naegleria	Worldwide	Freshwater sports	Acute meningoencephalitis
Acanthamoeba	Worldwide	Immunosuppression	Subacute or chronic meningoencephalitis

Figure 12-138. Protozoan infections of the nervous system. Protozoa are small, single-cell organisms that cause diffuse more often than focal encephalitis of the nervous system. Protozoa do not cause allergic reactions and eosinophilia as do many of the helminthic infections. (*Adapted from* Johnson and Warren [99].)

Clinical Manifestations of Toxiplasmosis

Congenital Disease	%	Immunocompromised Host	%
Retinochoroiditis	87	Altered mental state	75
Abnormal cerebrospinal fluid	55	Fever	10–72
Anemia	51	Seizures	33
Convulsions	50	Headache	56
Intracranial calcifications	50	Focal neurologic signs	60
Jaundice	29	Motor deficits	
Fever	25	Cranial nerve palsies	
Splenomegaly	21	Movement disorders	
Hepatomegaly	17	Dysmetria	
		Visual field loss	
		Aphasia	

Figure 12-139. Clinical manifestations of toxoplasmosis. Congenital toxoplasmosis is a systemic illness causing chorioretinitis, microencephaly, seizures, mental retardation (from encephalitis), and cerebral calcifications in newborns. Cases in immunocompromised patients are frequent, thus, toxoplasmosis is a common opportunistic infection in AIDS patients that usually occurs because of reactivation. (*Adapted from* Luft and Remington [100].)

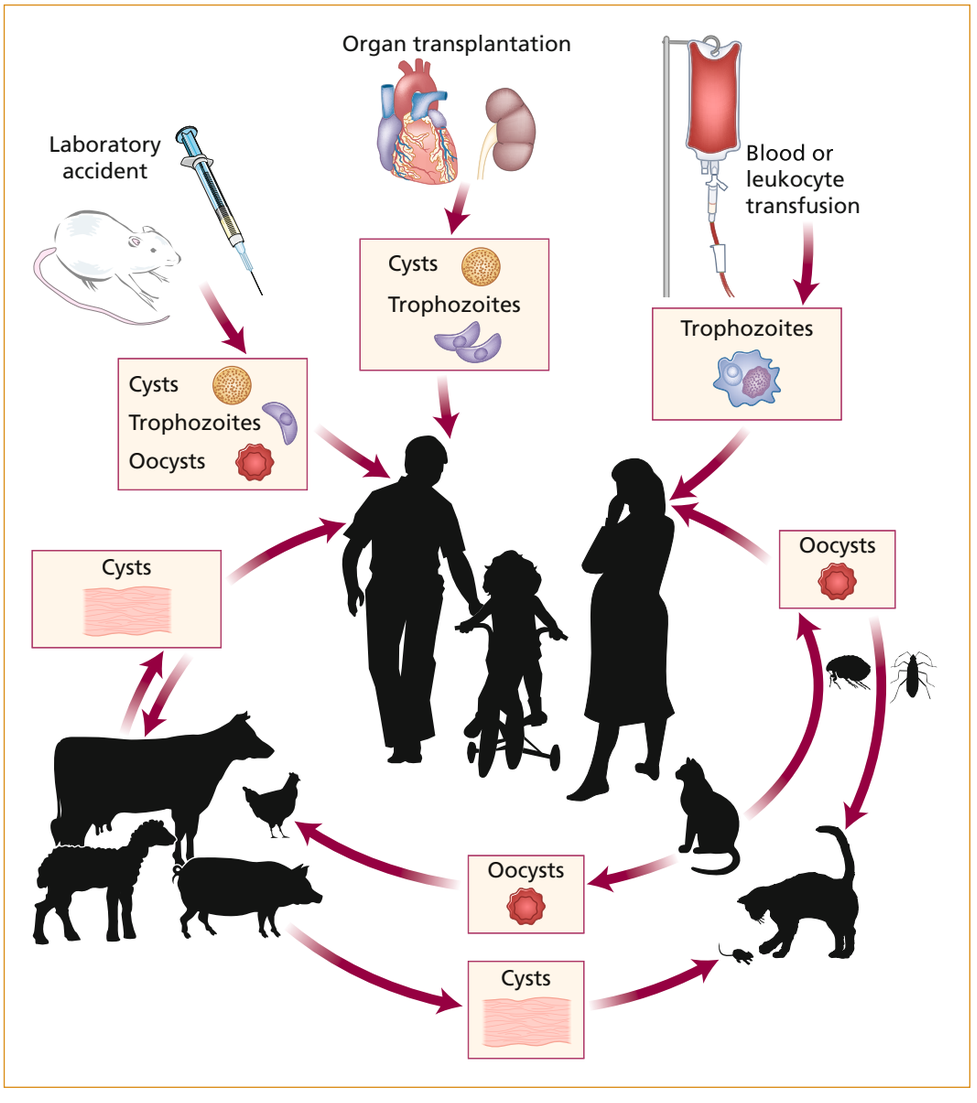


Figure 12-140. Transmission of toxoplasmosis. Most often *Toxoplasma gondii* infection occurs by eating undercooked meat or other foods contaminated with cat feces containing oocysts. Common-source outbreaks have occurred in families from contaminated food. Unpasteurized milk and water are also possible sources of infection. In addition to exposure to cats and eating undercooked meats, warm humid climates and poor sanitation correlate with a greater prevalence of infection. Primary infection in the immunocompetent host is usually asymptomatic. Rarely, symptomatic severe primary infection occurs. Usually tissue cysts persist and reactivation is prevented unless immunity wanes, as occurs in AIDS or other immunosuppressive events (such as therapy for cancer and transplantation). (*Adapted from* Berger [101].)

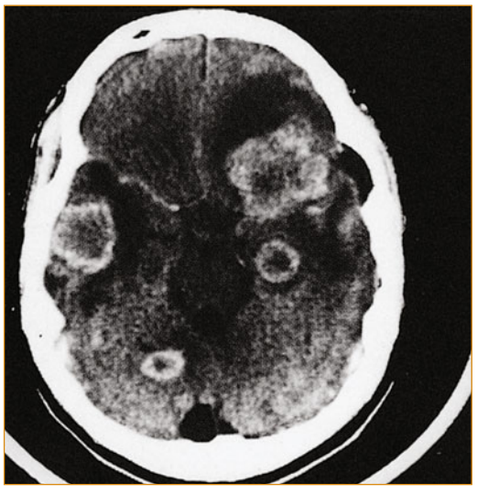


Figure 12-141. Enhanced axial CT of toxoplasmosis in an AIDS patient showing multiple ring and nodular enhancing lesions. The complete blood count may reveal anemia, leukopenia, or leukocytosis in congenital toxoplasmosis. In most AIDS patients, disease is limited to the brain. The cerebrospinal fluid (CSF) is abnormal in about half the patients with congenital toxoplasmosis and in most patients with AIDS. Lymphocytic pleocytosis is usually mild but may be as high as several thousand cells/mm^3. The protein level is increased and the glucose level is usually normal or rarely mildly reduced. Isolation of the organism is difficult, as it requires inoculation of laboratory mice; therefore, a presumptive diagnosis can be made based on serologic tests in the appropriate clinical setting. The demonstration of IgM antibodies is most helpful for the diagnosis of congenital or acute acquired infection. In AIDS and other immunosuppressed patients, IgG, but not IgM, antibody is usually present. CSF antibodies may also be detected. Other than serologic testing, neuroimaging is the diagnostic study of choice. In congenital toxoplasmosis the skull radiograph may reveal multiple intracerebral calcifications. T1-weighted MRI of toxoplasmosis in AIDS patients reveals multiple ring enhancing, hypodense lesions with surrounding edema as does the CT scan shown here. Polymerase chain reaction of the CSF is not very sensitive at this time. (*From* Farrar *et al*. [102]; with permission.)

Guidelines for Treatment of Toxoplasma Encephalitis in AIDS

Drug	Dosage Schedule
Standard regimens	
Pyrimethamine	Oral, 200 mg loading dose, then 50 to 75 mg daily
Folinic acid (leucovorin)	Oral, IV, or IM, 10–20 mg daily (up to 50 mg daily)
plus	
Sulfadiazine	Oral, 1–1.5 g q6h
or	
Clindamycin	Oral or IV, 600 mg q6h (up to IV 1200 mg q6h)
Possible alternative regimens	
Trimethoprim/sulfamethoxazole	Oral or IV 5 mg (trimethoprim component)/kg q6h
Pyrimethamine and folinic acid	As in standard regimens plus one of the following:
Clarithromycin	Oral, 1 g q12h
Azithromycin	Oral, 1200–1500 mg daily
Atovaquone	Oral, 750 mg q6h
Dapsone	Oral, 100 mg daily

Figure 12-142. Guidelines for treatment of toxoplasma encephalitis in AIDS. The prognosis is poor in the congenital form of toxoplasmosis, with death occurring within weeks of birth in more than 50% of cases. Mental retardation and other neurologic defects are common in survivors. The prognosis for reactivated infections in immunocompromised patients is also poor. In AIDS patients, empiric therapy is instituted when IgG antibody and characteristic CT findings are found. Pyrimethamine and sulfadiazine are the agents of choice. IM—intramuscular; IV—intravenous. (*Adapted from* Montoya *et al*. [103].)

Cerebral Malaria

Clinical Manifestations of Cerebral Malaria

Common	Less Common	Possible Systemic Manifestations
Headache, meningismus, photophobia	Monoparesis and hemiparesis	Hyperpyrexia
Seizures	Aphasia	Anemia
Behavioral and cognitive changes	Hemianopia	Hepatosplenomegaly
Delirium	Ataxia, tremor, myoclonus	Hypoglycemia
Coma	Cranial nerve palsies	Disseminated intravascular coagulation
	Papilledema	Pulmonary edema
	Blindness	Renal failure
	Deafness	Shock
	Spinal cord lesions	
	Polyneuritis	

Figure 12-143. Clinical manifestations of cerebral malaria. The symptoms and signs of cerebral malaria are primarily those of acute encephalopathy. These neurologic manifestations usually occur in the second or third week of infection. The disease occurs most often in infants, children, and nonimmune travelers to endemic areas. (*Adapted from* Berger [101].)

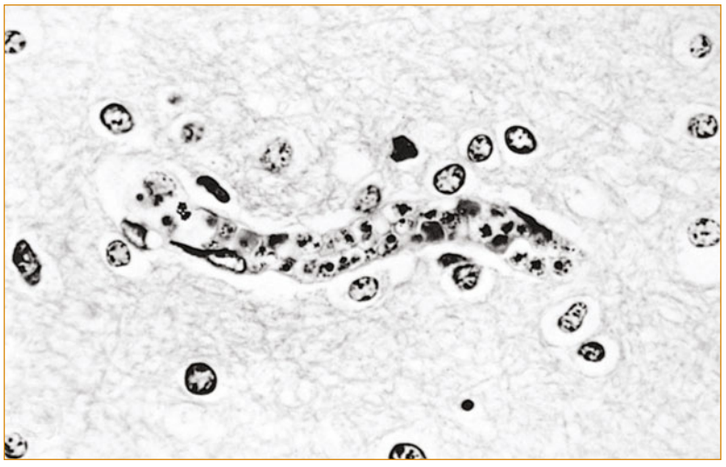


Figure 12-144. A brain capillary with parasitized erythrocytes in a patient with cerebral malaria. The neurologic manifestations are due to the congestion and obstruction of capillaries and venules with parasitized erythrocytes. Parasitized erythrocytes are less deformable than normal erythrocytes and more adherent to vascular endothelial cells. Thrombotic occlusions, microinfarctions, microhemorrhages, and cerebral edema result. Large infarctions and hemorrhage are unusual.

Malaria is the most common human parasitic disease in the world. In 2002, there were about 515 million people in the world infected with malaria, 70% in Africa and 25% in Southeast Asia. The yearly death rate is 2 million. The disease is endemic in tropical and subtropical areas of Asia, Africa, and Central and South America. Nervous system involvement occurs in about 2% of infected patients. Cerebral malaria is caused only by *Plasmodium falciparum*. (*From* Oo *et al*. [104]; with permission.)

Antimalarial Therapy for Cerebral Malaria

	Route	Indication	Loading Dose	Maintenance Dose
Quinine dihydrochloride	IV	Children and adults	20 mg/kg over 2–4 h (max 600 mg)	10 mg/kg every 8 h until able to take orally
Quinine dihydrochloride	IV	Children	15–20 mg/kg over 2–4 h	10 mg/kg every 12 h until able to take orally
Quinine dihydrochloride	IM	Children and adults	20 mg/kg (dilute IV formulation to 60 mg/mL) given in two injection sites (anterior thigh)	10 mg/kg every 8–12 h until able to take orally
Quinidine gluconate	IV	Children and adults	10 mg/kg in normal saline over 1–2 h	0.02 mg/kg/min continuous infusion with electrocardiogram monitoring up to 72 h or 10 mg/kg every 8–12 h
Artemether	IM	Children and adults	3.2 mg/kg	1.6 mg/kg/d for a minimum of 5 days
Artemether	IV/IM	Children and adults	2.4 mg/kg	1.2 mg/kg after 12 and 24 h then 1.2 mg/kg/d for 7 days; change to oral route when possible

Figure 12-145. Treatment of cerebral malaria. Diagnosis is made from the clinical presentation and by finding the organisms in the blood. The mortality rate for cerebral malaria is 15% to 40%, with the highest mortality rate in those patients with coma and seizures. Treatment has classically been with chloroquine, but chloroquine-resistant falciparum malaria requires treatment with quinine plus sulfadoxine/pyrimethamine. IM—intramuscular; IV—intravenous. (*Adapted from* Idro *et al*. [105].)

Trypanosomiasis

Comparison of West African and East African Trypanosomiasis

	West African *(T. gambiense)*	East African *(T. rhodesiense)*
Organism	*T.b. gambiense*	*T.b. rhodesiense*
Vectors	Tsetse flies (*palpalis* group)	Tsetse flies (*morsitans* group)
Primary reservoir	Humans	Antelope and cattle
Human illness	Chronic (late CNS disease)	Acute (early CNS disease)
Duration of illness	Months to years	< 9 months
Lymphadenopathy	Prominent	Minimal
Parasitemia	Low	High
Diagnosis by rodent inoculation	No	Yes
Epidemiology	Rural populations	Tourists in game parks
		Workers in wild areas
		Rural populations

Figure 12-146. Comparison of West African and East African trypanosomiasis. There are two varieties of human trypanosomiasis, an African form (sleeping sickness) and a South American form (Chagas disease), which is caused by *Trypanosoma cruzi*. The African disease is of two types. The West African form is caused by *Trypanosoma brucei gambiense* and the East African variety by *Trypanosoma brucei rhodesiense*. The East African disease is more acute, leading to death in weeks to months. CNS—central nervous system. (*Adapted from* Kirchhoff [106].)

Clinical Manifestations of African Trypanosomiasis

Stage I—febrile or hemolymphatic stage	Stage II—lethargic or meningoencephalitic stage
Remitting fever	Headache
Circinate rash and pruritus	Irritability
Lymphadenitis	Personality change with apathy
Transient edema of face and hands	Organic mental syndrome
Hepatosplenomegaly	Insomnia or somnolence
Headache	Tremor
Asthenia	Ataxia
Arthralgia	Convulsions
Myalgia	Paralysis
Weight loss	Coma

Figure 12-147. Clinical manifestations of African trypanosomiasis. The signs and symptoms of West and East African trypanosomiasis are basically the same, except that the East African form has a more acute course of weeks to months while the West African form has a more chronic course of months to years. These diseases pass through two stages: stage I is the systemic illness, with organisms present in the blood; stage II is neurologic. The first stage usually passes imperceptibly into the second.

Clinical Manifestations of South American Trypanosomiasis

Acute stage	Chronic stage
Fever	Cardiac disease
Conjunctivitis	Gastrointestinal disease
Palpebral and facial edema	Mental alterations
Lymphadenopathy	Convulsions
Hepatosplenomegaly	Choreoathetosis
Acute encephalitis (rare)	Hemiplegia
	Ataxia
	Aphasia

Figure 12-148. Clinical manifestations of South American trypanosomiasis. The acute stage lasts about 1 month, during which trypanosomes are present in the blood. In the chronic stage, organ involvement including the nervous system occurs. This disease affects about 16 million people in Central and South America, primarily children living in rural areas. The disease is transmitted by the reduviid bug, which lives in the walls of houses. Death usually occurs within a few months or years.

Treatment of Human Trypanosomiasis

African trypanosomiasis

Hemolymphatic (stage I)

Suramin, 100–200 mg test dose IV, *then* 1g IV on days 1, 3, 7, 14, 21

or

Eflornithine, 100 mg/kg qid × 14 d, *then* 300 mg/kg/d po × 3–4 wk

CNS involvement (stage II)

West African

Eflornithine, 100 mg/kg qid × 14 d, *then* 300 mg/kg/d po × 3–4 wk

East African

Melarsoprol, 2–3.6 mg/kg/d IV in 3 doses × 3 d, *then*, after 1 wk, 3.6 mg/kg/d IV in 3 doses × 3 d, repeat after 7 days

American trypanosomiasis

Nifurtimox, 8–10 mg/kg/d po in 4 doses × 90–120 d

Figure 12-149. Diagnosis and treatment of trypanosomiasis. Anemia occurs in all forms of trypanosomiasis. The erythrocyte sedimentation rate and serum IgM may be increased. The cerebrospinal fluid (CSF) has lymphocytic pleocytosis, normal glucose level, increased protein level, and increased IgG and IgM levels. The diagnosis is established by identifying the organism in the blood, CSF, or biopsied lymph nodes. Except for the chronic stage of American trypanosomiasis, chemotherapy is relatively effective. CNS—central nervous system; IV—intravenous; po—per os (by mouth). (*Adapted from* Berger [101].)

Species of Amebae Causing Amebic Meningoencephalitis

Taxonomy	Host	Pathogen	Disease
Order Amoebida			
Family Endamoebidae			
Entamoeba histolytica	Humans	Yes	Colitis, hepatic, lung, and brain abscess
Endolimax nana	Humans	No	None
Iodamoeba butschlii	Humans	No	None
Family Acanthamoebidae			
A. culbertsoni, A. polyphaga, A. castellani, A. astronyxis, A. palestinensis, A. rhysodes, others	Humans, mice	Yes	GAE, keratoconjunctivitis, skin lesions, mandibular bone graft infection
Order Schizopyrenida			
Family Vahlkampfidae			
Naegleria fowleri	Yes	Humans	PAM
Naegleria australiensis	Yes	Mice	Experimental PAM
Naegleria gruberi, Naegleria lovaniensis	No	None known	None known
Vahlkampfia	Unproven	? Humans	? GAE or PAM
Order Leptomyxida			
Balamuthia mandrillaris	Yes	Humans, primates, sheep	GAE
Leptomyxa	No	?	?

Figure 12-150. Species of amebae causing amebic meningoencephalitis. The species primarily causing meningoencephalitis are the free-living amebae *Naegleria fowleri* and *Acanthamoeba* species. *Entamoeba histolytica* may rarely invade the brain and cause brain abscess. *Naegleria* causes acute primary amebic meningoencephalitis (PAM), whereas *Acanthamoeba* causes subacute or chronic PAM and granulomatous amebic encephalitis (GAE). The Leptomyxida *Balamuthia mandrillaris* has also caused GAE. These infections occur worldwide. Most cases in the United States occur in the Southeast. (*Adapted from* Durack [107].)

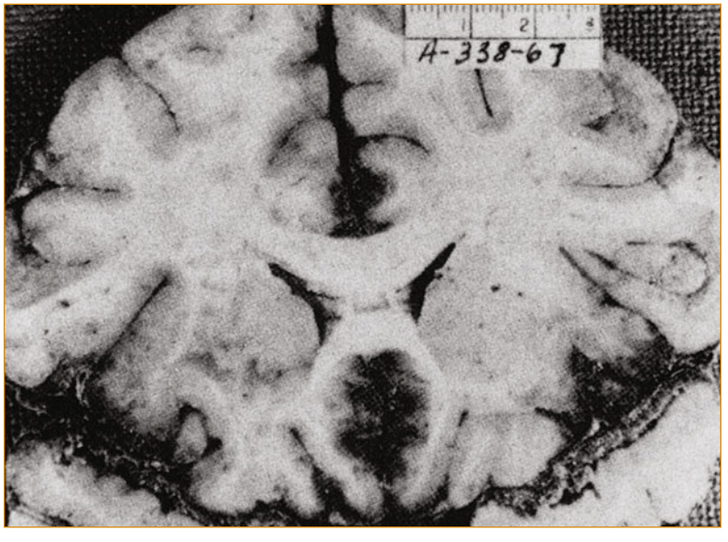


Figure 12-151. Acute primary amebic meningoencephalitis (PAM), with the most severe lesions in the basal meninges and adjacent cortex. *Acanthamoeba* causes subacute or chronic PAM, including granulomatous amebic encephalitis (GAE), usually as an opportunistic infection in immunosuppressed patients. The respiratory tract is probably the portal of entry, resulting in systemic infection with seeding of the brain through hematogenous spread. GAE may ensue with multiple focal areas (cortical, subcortical white matter, and basal ganglia) of infection.

Naegleria infections usually occur in children and young adults who have been swimming in fresh water lakes and ponds, although inhalation of dust-borne cysts occurs in arid regions. The organism does not cause a systemic infection but invades the brain through olfactory nerves. (*From* Durack [107]; with permission.)

Clinical Manifestations of Primary Amebic Meningoencephalitis

Acute	Subacute or Chronic, Including Granulomatous
Abrupt onset	Insidious onset
Fever	Chronic fever
Headache	Headache
Nuchal rigidity	Gradual onset of focal signs
Vomiting	Aphasia
Lethargy	Focal seizures
Disorientation	Hemiparesis
Seizures	Ataxia
Increased intracranial pressure	Altered mentation
Coma	Systemic manifestations
	Skin lesions
	Corneal ulcers
	Uveitis
	Pneumonitis

Figure 12-152. Clinical manifestations of primary amebic meningoencephalitis (PAM). Acute PAM caused by *Naegleria* presents as acute meningoencephalitis after an incubation period of several days to a week. The cerebrospinal fluid (CSF) profile is similar to that of acute bacterial meningitis, with several hundred to thousand leukocytes, primarily polymorphonuclear leukocytes, and a low glucose level. Amebae may be seen on wet preparations or with Wright or Giemsa stains. The organisms can be cultured on special media or isolated by mouse inoculation. A serologic test is available at the Centers for Disease Control and Prevention. The disease is rapidly fatal. Amphotericin B is the drug of choice. Subacute or chronic PAM (including granulomatous amebic encephalitis) presents more gradually, similar to a brain abscess or tumor. The CSF pleocytosis is more often lymphocytic, with a normal or only slightly decreased glucose level. Amebae can be found in the CSF only occasionally. Neuroimaging reveals focal lesions; biopsy is usually required for diagnosis. This disease is usually fatal. In vitro the organism is usually sensitive to pentamidine, ketoconazole, and flucytosine.

Helminthic Infections

Nematode (Roundworm) Infections of the Nervous System

Disease/Parasite	Geographic Distribution	Risk Factors	Neurologic Disease
Trichinella spiralis	Worldwide	Eating rare pork or bear meat	Acute meningoencephalitis myositis
Angiostrongylus cantonensis	Southeast Asia, Oceania	Eating freshwater snails, crabs, and raw vegetables	Acute eosinophilic meningitis
Gnathostoma	Japan, Thailand, Phillippines, Taiwan	Eating raw fish or meat	Hemorrhages, infarcts (rare)
Strongyloides	Tropics	Penetration of skin or gut by filariform; dissemination with immunosuppression	Meningitis (rare), paralytic ileus due to autonomic involvement
Toxocara	Worldwide	Children with pica, contamination with dog or cat feces	Small granulomas (rare), ocular granuloma
Filaria loa loa	Tropical Africa	Bites by deer flies, horseflies	Acute cerebral edema, subacute encephalitis (rare)
Onchocerca volvulus	Equatorial Africa, Latin America	Black flies	Chorioretinal lesions

Figure 12-153. Nematode (roundworm) infections of the nervous system. These infections are no longer common in the United States or other developed countries. Trichinosis was common in the United States during the first half of the twentieth century but is now almost nonexistent because of improved sanitation and public health measures. Mebendazole or albendazole is used to treat tissue larvae. *Angiostrongylus* causes eosinophilic meningitis with headache, paresthesia, and a mean cerebrospinal fluid leukocyte count of 500 to 600 cells/mm^3, of which the mean eosinophil count is approximately 50%. Most patients recover in 1 to 2 weeks. Additional causes of eosinophilic meningitis include other helminths, coccidioidomycosis, foreign bodies, drug allergies, and neoplasia. The other roundworm infections less frequently involve the nervous system. (*Adapted from* Johnson and Warren [99].)

Trematode (Fluke) Infections of the Nervous System

Disease/Parasite	Geographic Distribution	Risk Factors	Neurologic Disease
Schistosomiasis			
Schistosoma japonicum	Far East	Walking or swimming in infested waters (snails)	Cerebral granulomas
Schistosoma mansoni	South America, Caribbean, Africa		Myelitis (rare)
Schistosoma hematobium	Africa, Middle East		Myelitis (rare)
Paragonimus sp.	Asia, Central Africa, Central and South America	Eating infected freshwater crabs and crayfish	Cerebral granulomas

Figure 12-154. Trematode (fluke) infections of the nervous system. Many species of trematodes can infect humans, although schistosomiasis and paragonimiasis are the most common. With the exception of some schistosomes, most trematodes have wild or domestic animals as definitive hosts, with humans infected accidentally. Eosinophilia is common during acute trematode infections. *Paragonimus* are lung flukes, the lungs being the final habitat. Acute purulent (meningoencephalitic) forms, chronic granulomatous (tumorous) forms, and late inactive forms are seen. In the acute meningoencephalitic form, there is fever, headache, seizures, hemiparesis and other focal deficits, and confusion. The cerebrospinal fluid pleocytosis consists of polymorphonuclear leukocytes in the acute form and lymphocytes in the chronic form. Eosinophils occasionally appear in the cerebrospinal fluid. Serologic tests are generally available. Diagnosis is confirmed by finding ova in the stool or sputum or by biopsy. CT may reveal "soap bubble" calcifications. The acute form has a 10% mortality rate; the chronic form is benign. The acute form is treated with praziquantel or bithionol; the chronic form, with surgery. (*Adapted from* Johnson and Warren [99].)

Species of *Schistosoma* that Infect Humans

	Intermediate Hosts		
Species Infecting Humans	**Primary**	**Secondary**	**Final Habitat**
S. haematobium	Snails	None	Vesical plexus
S. japonicum	Snails	None	Superior mesenteric veins
S. mansoni	Snails	None	Inferior mesenteric veins
S. mekongi	Snails	None	Mesenteric veins
S. intercalatum	Snails	None	Mesenteric veins

Figure 12-155. Species of *Schistosoma* that infect humans. Five species of this trematode infect over 200 million people in the world. It is estimated that over 400,000 cases exist in the United States, primarily in immigrants from infected areas (Puerto Rico, Brazil, Philippines, Middle East). Fortunately, the organism cannot be transmitted in this country because of the absence of the appropriate male intermediate host. *Schistosoma* are blood flukes; their final habitat is veins or venous plexi. The predilection for a specific region of the central nervous system (CNS) appears to relate to the location of the adult worms when ova are released. *S. japonicum* resides in the superior mesenteric veins; it infects the CNS in about 3% of cases. The small eggs of this organism are able to reach the brain; ectopic worms have been found in cerebral veins. *S. mansoni* and *S. haematobium*, residing in the inferior mesenteric veins and vesical plexus, respectively, have larger eggs that most commonly affect the spinal cord. This CNS involvement occurs less frequently than that seen with *S. japonicum*. Neurologic disease has not been well characterized for *S. mekongi* and *S. intercalatum*. (*Adapted from* Maguire [108].)

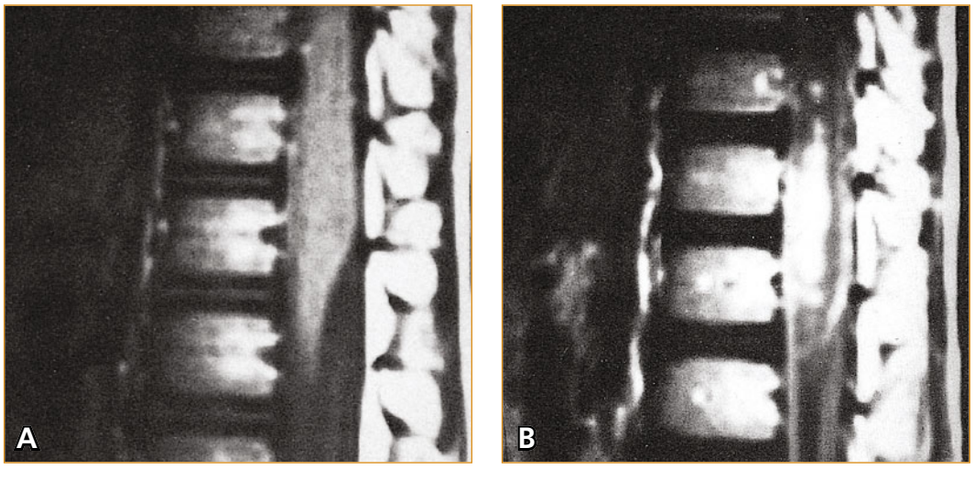


Figure 12-156. T1-weighted MRI showing sagittal view of a spinal cord in a case of *Schistosoma mansoni*. **A**, Precontrast MRI scan showing increased anteroposterior diameter of the spinal cord at T11–T12. **B**, Postcontrast MRI scan showing enhancement of the schistosomal lesion. Cerebral schistosomiasis may be acute or chronic. The acute form presents as fulminating meningoencephalitis with fever, headache, confusion, lethargy, seizures, focal deficits, and coma.

Continued on the next page

Figure 12-156. *(Continued)* The presentation of the chronic cerebral form is similar to a tumor, with focal deficits, seizures, increased intracranial pressure, and papilledema. The spinal cord disease is almost always acute, presenting as incomplete transverse myelitis. There is a peripheral leukocytosis with eosinophilia except in the chronic cerebral form. The cerebrospinal fluid shows slight to moderate pleocytosis, sometimes with eosinophilia. Cerebral lesions may be seen with CT or MRI; spinal lesions are seen with MRI or myelography. Diagnosis can be made by finding ova in the stool or urine, by using serologic tests, and rectal mucosal biopsy. Treatment includes the use of praziquantel, corticosteroids for edema, anticonvulsants for seizure, and often decompressive laminectomy for a spinal block. Oxamniquine may need to be added for *S. mansoni* species resistant to praziquantel. (*From* Selwa *et al*. [109]; with permission.)

Cestode (Tapeworm) Infections of the Nervous System

Disease/Parasite	Geographic Distribution	Risk Factors	Neurologic Disease
Cysticercosis			
Taenia solium	Central and South America, Asia, Africa, East Europe	Ingestion of eggs in human fecal contamination	Small cysts or basilar arachnoiditis with hydrocephalus; ocular lesions
Hydatid disease			
Echinococcus granulosus	Worldwide	Ingestion of eggs in canine fecal contamination	Large cysts
Coenurosis			
Multiceps multiceps	Europe, Americas	Ingestion of eggs in carnivore fecal contamination	Budding cysts (rare)

Figure 12-157. Cestode infections of the nervous system. Cestode, or human tapeworm, infections can be divided into two groups. In the first, humans are the definitive host and the adult worms (*Taenia saginata* and others) live in the gastrointestinal tract and the central nervous system (CNS) is not involved. In the second group, humans are the intermediate host and the larvae spread to the tissues, including the CNS (echinococcosis, coenurosis, and others less common). In *Taenia solium*, the pork tapeworm infection, humans may be either the definitive host (*T. solium*) or the intermediate host (cysticercosis).

Ingestion of undercooked pork containing the encysted larvae (*Cysticercus cellulosae*; tissue larval stage) results in infection of the human intestine by the adult tapeworm (definitive host). There are usually no symptoms at this stage. The terminal gravid proglottids of the worm are excreted in the feces with thousands of ova. These ova contaminate the environment, where they are ingested by pigs or humans (intermediate hosts). The shells of these eggs are digested by gastric juices, liberating the embryos (oncospheres), which penetrate the intestinal wall, migrate to tissues, and become encysted (cysticerci). In humans they primarily localize to the brain and CNS. Cysticercosis is clearly the most important cestode infection of humans. Coenurosis is the rare larval disease caused by the dog tapeworm, *Taenia* (*Multiceps*) *multiceps*. (*Adapted from* Johnson and Warren [99].)

Clinical Manifestations of Neurocysticercosis

Symptoms and Signs	Approximate Frequency, %
Headache	23–98
Seizures	37–92
Papilledema	48–84
Meningeal signs	29–33
Nausea/vomiting	74–80
Altered mental status	9–47
Dementia	1–6
Psychosis	1–17
Focal sensory or motor deficits	3–36
Cranial nerve palsies	1–36
Altered vision	5–34
Ataxia	5–24
Spinal cord compression	< 1

Figure 12-158. Clinical manifestations of neurocysticercosis. The manifestations of neurocysticercosis depend on the location of the lesions. The clinical disease can be divided into four types based on the anatomic location of infection: parenchymal, subarachnoid (meningitic), intraventricular, and spinal. In the parenchymal form, the manifestations are related to the location of the cysts. Focal seizures and focal neurologic deficits are seen in the parenchymal form. The meningitic form results in headache, nuchal rigidity, and communicating hydrocephalus. Intraventricular disease may result in obstructive hydrocephalus. Spinal disease may result in arachnoiditis and subarachnoid block. (*Adapted from* Cameron and Durack [110].)

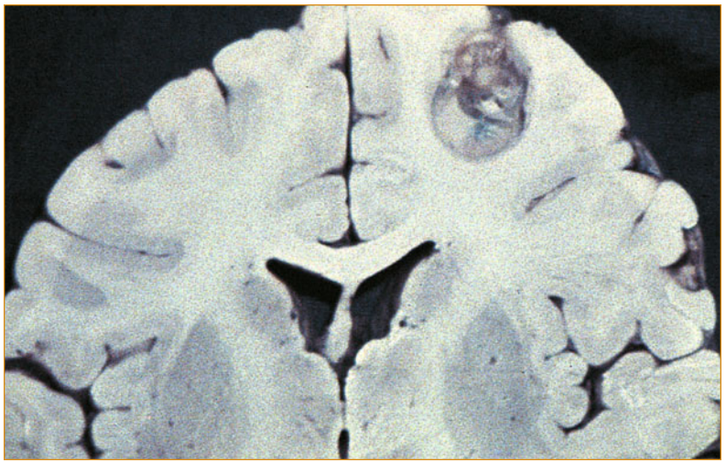


Figure 12-159. Pathologic sample showing the parenchymal cysticerci that are typically found at gray-white matter junctions. The encysted larvae (cysticerci) are fluid-filled cysts that may be deposited in parenchymal cerebrospinal fluid (CSF) spaces, where they may displace or compress tissue or block CSF pathways. (*From* Berger [101]; with permission.)

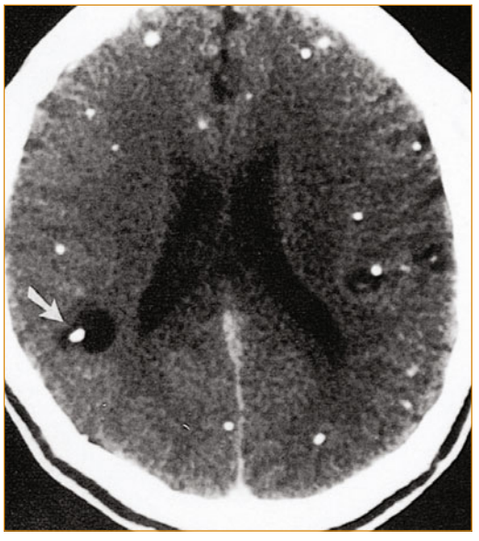


Figure 12-160. Noncontrast CT scan showing numerous calcified (inactive) cysticerci and an active cyst with scolex (*arrow*) with contrast ring enhancement of active cysts in a patient with neurocysticercosis. The diagnosis of cysticercosis should be considered in patients who reside in endemic areas (*see* Fig. 12-157) and have seizures, meningitis, or papilledema (increased intracranial pressure). CT and MRI are especially useful, as they may demonstrate live parenchymal cysts with enhancement (diffuse or ring pattern), calcified dead cysts, hydrocephalus, and intraventricular and subarachnoid cysts with enhancement. Usually the cerebrospinal fluid (CSF) shows mild pleocytosis, but may be normal or show severe pleocytosis due to meningitis when subarachnoid or intraventricular cysts die. There may be up to several thousand leukocytes (usually mononuclear), a low glucose level, and an elevated protein level. CSF and serum antibody tests are usually positive (80% to 98% sensitivity depending on the test). (*From* Cameron and Durak [110]; with permission.)

Treatment of Neurocysticercosis

Medical therapy	
Praziquantel	50 mg/kg/d in 3 doses × 15 d
Albendazole	15 mg/kg/d in 3 doses × 8 d
Plus adjunctive corticosteroids	
or	
Surgical excision	

Figure 12-161. Treatment of neurocysticercosis. For symptomatic patients, both praziquantel and albendazole are effective. Because dying cysticerci provoke a severe inflammatory reaction with edema, corticosteroids should be used concomitantly. Seizures can usually be controlled with anticonvulsants, but if intractable, surgical removal of cysts may be required. Ventricular shunting is usually adequate for hydrocephalus. Symptomatic ocular and spinal lesions usually require surgical excision. (*Adapted from* Berger [101].)

Clinical Manifestations of CNS Echinococcosis
Headache
Increased intracranial pressure
Nausea and vomiting
Papilledema
Seizures
Focal neurologic signs
Hemiparesis
Hemisensory loss
Aphasia
Ataxia
Cranial nerve palsies
Spinal cord compression

Figure 12-162. Clinical manifestations of central nervous system (CNS) echinococcosis (hydatid disease, hydatid cysts). Echinococciasis is the tissue infection caused by the larvae of a dog tapeworm. Most cases are caused by *Echinococcus granulosus*, but a few have been caused by *Echinococcus multilocularis*, *Echinococcus vogeli*, and *Echinococcus oligarthrus*. The disease primarily occurs in sheep-herding regions of Africa, South America, Eastern Europe, the former Soviet Union, and the Mediterranean. Sheep and cattle are the usual intermediate hosts. In the brain, the disease presents as a slowly expanding mass lesion.

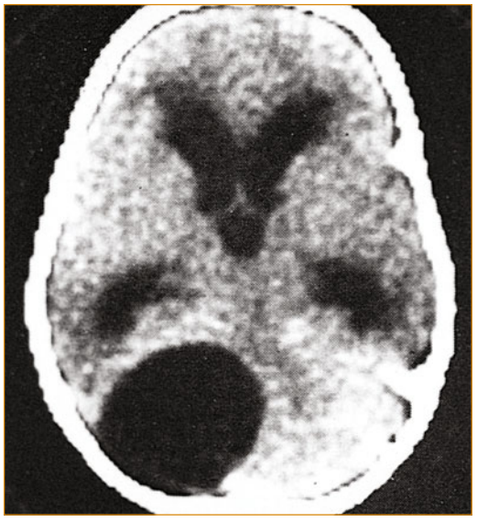


Figure 12-163. CT scan of a patient with a hydatid cyst of the brain. CT and MRI scans localize the lesions, which are usually single, nonenhancing, and have the density of cerebrospinal fluid. Needle biopsy is usually precluded because of severe allergic reactions, including anaphylaxis, caused by cyst rupture. Additional cysts may be found in the lungs and liver. The enzyme-linked immunosorbent assay antibody test has a 95% sensitivity. Surgical removal of cysts is the preferred treatment. Drug treatment with albendazole may decrease the size of the cysts, but it should be started before surgery to prevent allergic reactions and secondary hydatidosis at the time of surgery. (*From* Abbassioun *et al*. [111]; with permission.)

References

1. Roos KL, Tunkel AR, Scheld WM: Acute bacterial meningitis in children and adults. In *Infections of the Central Nervous System*, edn 2. Edited by Scheld WM, Whitley RJ, Durack PT. Philadelphia: Lippincott-Raven; 1997:335–401.
2. Roos KL, Bonnin JM: Acute bacterial meningitides. In *Atlas of Infectious Diseases: Central Nervous System and Eye Infections*, vol 3. Edited by Mandell GL, Bleck TP. Philadelphia: Current Medicine; 1995:1.2–1.25.
3. Kaplan MH: Part 1: Bacterial and viral causes. In *Meningitis and CNS Infection*. Garden Grove, CA: Medcom; 1979: Slide 2.
4. Wilson N: Infections of the nervous system. In *Neuropathology: An Illustrated Course*. Edited by Duffy PE. Philadelphia: FA Davis; 1977: Slide 12.
5. Durand ML, Calderwood SB, Weber DJ, *et al*.: Acute bacterial meningitis in adults: a review of 493 episodes. *N Engl J Med* 1993, 328:21–28.
6. Gold R: Epidemiology of bacterial meningitis. *Infect Dis Clin North Am* 1999, 13:515–525.
7. Rosenstein NE, Perkins BA: Update on Haemophilus influenzae serotype b and meningococcal vaccines. *Pediatr Clin North Am* 2000, 47:337–352.
8. Schuchat A, Robinson K, Wenger JD, *et al*.: Bacterial meningitis in the United States in 1995. *N Engl J Med* 1997, 14:970–976.
9. Roos K, Tunkel AR, Scheld WM: Acute bacterial meningitis. In *Infections of the Central Nervous System*, edn 3. Edited by Scheld WM, Whitley RJ, Marra CM. Philadelphia: Lippincott Williams & Wilkins; 2004:347–422.
10. Schaad UB, Lips U, Gnehm HE, *et al*.: Dexamethasone therapy for bacterial meningitis in children. Swiss Meningitis Study Group. *Lancet* 1993, 342:457–461.
11. van de Beek D, de Gans J, McIntyre P, Prasad K: Steroids in adults with acute bacterial meningitis: a systemic review. *Lancet Infect Dis* 2004, 4:139–143.
12. Centers for Disease Control and Prevention: Recommended childhood immunization schedule—United States 2002. *MMWR* 2002, 51:31–33.
13. Centers for Disease Control and Prevention: Prevention and control of meningococcal disease. Recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR* 2000, 49(RR-7):1–10.
14. British Medical Research Council: Streptomycin treatment of tuberculosis meningitis. *Lancet* 1948, 1:482–596.
15. Zuger A, Lowy FD: Tuberculosis of the central nervous system. In *Infections of the Central Nervous System*, edn 2. Edited by Scheld WM, Whitley RJ, Durack DT. Philadelphia: Lippincott-Raven; 1997:417–443.
16. Zuger A: Tuberculosis. In *Infections of the Central Nervous System*, edn 3. Edited by Scheld WM, Whitley RJ, Marra CM. Philadelphia: Lippincott Williams & Wilkins; 2004:441–459.
17. Rafi W, Venkataswamy MM, Ravi V, Chandramuki A: Rapid diagnosis of tuberculous meningitis: a comparative evaluation of in-house PCR assays involving three mycobacterial DNA sequences, IS6110, MPB-64, and 65 kDa antigen. *J Neurol Sci* 2007, 252:163–168.

18. American Thoracic Society joint statement. Treatment of tuberculosis. *Am J Respir Crit Care Med* 2003, 167:603–662.
19. Kumar R, Prakash M, Jha S: Paradoxical response to chemotherapy in neurotuberculosis. *Pediatr Neurosurg* 2006, 42:214–222.
20. Kennedy DH, Fallon RJ: Tuberculous meningitis. *JAMA* 1979, 241:264–268.
21. Weisberg L, Nice C, Katz M: Infectious inflammatory conditions. In *Cerebral Computed Tomography: A Text Atlas*, edn 2. Philadelphia: WB Saunders; 1984:229–248.
22. Danner RL, Hartman BJ: Update of spinal epidural abscess: 35 cases and review of the literature. *Rev Infect Dis* 1987, 9:265–274.
23. Gelfand MS, Bakhtian BJ, Simmons BP: Spinal sepsis due to *Streptococcus milleri*: two cases and review. *Rev Infect Dis* 1991, 13:559–563.
24. Hartman BJ, Helfgott DC, Weingarten K: Subdural empyema and suppurative intracranial phlebitis. In *Infections of the Central Nervous System*, edn 3. Edited by Scheld WM, Whitley RJ, Marra CM. Philadelphia: Lippincott Williams & Wilkins; 2004:524–535.
25. Greenlee JE: Subdural empyema. In *Principles and Practice of Infectious Diseases*, edn 4. Edited by Mandell GL, Bennet JE, Dolin R. New York: Churchill Livingstone; 1995:900–903.
26. Wispelwey B, Dacey RG Jr, Scheld WM: Brain abscess. In *Infections of the Central Nervous System*, edn 2. Edited by Scheld WM, Whitley RJ, Durack DT. Philadelphia: Lippincott-Raven; 1997:463–493.
27. Wispelwey B, Scheld WM: Brain abscess. In *Principles and Practice of Infectious Diseases*, edn 4. Edited by Mandell GL, Douglas RG Jr, Bennett JE. New York: Churchill Livingstone; 1995:889–891.
28. Wispelwey B: Brain abscess. In *Atlas of Infectious Diseases: Central Nervous System and Eye Infections*, vol. 3 Edited by Mandell GL, Bleck TP. Philadelphia: Current Medicine; 1995:4.2–4.14.
29. Falcone S, Post MJ: Encephalitis, cerebritis, and brain abscess: pathophysiology and imaging findings. *Neuroimaging Clin North Am* 2000, 10:333–353.
30. Kastenbauer S, Pfister H–W, Wispelwey B, Scheld WM: Brain abscess. In *Infections of the Central Nervous System*, edn 3. Edited by Scheld WM, Whitley RJ, Marra CM. Philadelphia: Lippincott Williams & Wilkins; 2004:479–507.
31. Jubelt B: Viral infections. In *Merritt's Textbook of Neurology*, edn 9. Edited by Rowland LP. Philadelphia: Lippincott Williams & Wilkins; 2005:175–210.
32. Centers for Disease Control and Prevention: Annual summary 1981: reported morbidity and mortality in the United States. *MMWR* 1982, 30(54).
33. Read SJ, Kurtz JB: Laboratory diagnosis of common viral infectios of the central nervous system by using a single multiplex PCR screening assay. *J Clin Microbiol* 1999, 37:1352–1355.
34. Jubelt B: The diagnosis of viral meningitis and encephalitis. In *Neurology and Neurosurgery Update Series*, vol 2, no 30. Edited by Scheinberg P, Davidoff RA, Arnason BGW. Princeton NJ: Education Center; 1981.
35. Jubelt B, Lipton HL: Enterovirus infections. In *Handbook of Clinical Neurology*, vol 12. Edited by Vinken PJ, Bruyn GW, Klawans HL. Amsterdam: Elsevier Science Publishing; 1989:326.
36. Hanley DF, Glass JD, McArthur JC, Johnson RT: Viral encephalitis and related conditions. In *Atlas of Infectious Diseases: Central Nervous System and Eye Infections*. Edited by Mandell GL, Bleck TB. Philadelphia: Current Medicine; 1995:3.2–3.40.
37. Solomon T: Flavivirus encephalitis. *N Engl J Med* 2004, 351:370–378.
38. Whitley RJ, Alford CA, Hirsch MS, *et al*.: Vidarabine versus acyclovir therapy in herpes simplex encephalitis. *N Engl J Med* 1986, 314:144–149.
39. Skoldenberg B, Forsgren M, Alestig K, *et al*.: Acyclovir versus vidarabine in herpes simplex encephalitis. Randomised multicenter study in consecutive Swedish patients. *Lancet* 1984, 2:707–711.
40. Johnson RT: *Viral Infections of the Nervous System*. New York: Raven Press; 1998:133–168.
41. Hirano A, Iwato M, Kato T, *et al*.: *Color Atlas of Pathology of the Nervous System*, edn 2. Edited by Hirano A. Tokyo: Igaku-Shoin; 1998:133–168.
42. Davis JM, Davis KR, Kleinman GM, *et al*.: Computed tomography of herpes simplex encephalitis with clinicopathological correlation. *Radiology* 1978, 129:409–417.
43. Runge VM: Skull and its contents. In *Magnetic Resonance Imaging of the Brain*. Philadelphia: JB Lippincott; 1994:180.
44. Schroth G, Gawehn J, Thron A, *et al*.: Early diagnosis of herpes simplex encephalitis by MRI. *Neurology* 1987, 37:179–183.
45. Davis LE, DeBiasi R, Goade DE, *et al*.: West Nile virus neuroinvasive disease. *Ann Neurol* 2006, 60:286–300.
46. Robinson P: Rabies. In *Infectious Diseases*. Edited by Gorbach SL, Bartlett JG, Blacklow NR. Philadelphia: WB Saunders; 1992:1269–1277.
47. Rupprecht CE, Hemachudha T: Rabies. In *Infections of the Central Nervous System*, edn 3. Edited by Scheld WM, Whitley RJ, Marra CM. Philadelphia: Lippincott Williams & Wilkins; 2004:243–259.
48. Hanna JN, Carney IK, Smith GA, *et al*.: Australian bat lyssavirus infection: a second human case, with a long incubation period. *Med J Aust* 2000, 172:597–599.
49. Corey L: Rabies, rhabdoviruses, and Marburg-like agents. In *Harrison's Principles of Internal Medicine*, edn 13. Edited by Isselbacher KJ, Braunwald E, Wilson JD. New York: McGraw Hill; 1994:834.
50. Centers for Disease Control and Prevention: Human rabies prevention—United States, 1999. Recommendations of the Advisory Practices (ACIP). *MMWR* 1999, 48:1–21.
51. Centers for Disease Control and Prevention: Summary of notifiable disease, United States, 1993. *MMWR* 1993, 42(53):27.
52. Mihai C, Jubelt B: Post-infections encephalomyelitis. *Curr Neurol Neurosci Rep* 2005, 5:440–445.
53. Horstmann DM: Epidemiology of poliomyelitis and allied diseases—1963. *Yale J Biol Med* 1964, 36:5–26.
54. Jubelt B, Gallez-Hawkins G, Narayan O, Johnson RT: Pathogenesis of human poliovirus infection in mice. I. Clinical and pathological studies. *J Neuropathol Exp Neurol* 1980, 39:138–148.
55. Kincaid O, Lipton HL: Viral myelitis: an update. *Curr Neurol Neurosci Rep* 2006, 6:469–474.
56. Anders HJ, Goebel FD: Cytomegalovirus polyradiculopathy in patients with AIDS. *Clin Infect Dis* 1998, 27:345–352.
57. Talpes D, Tien RD, Hesselink JR: Magnetic resonance imaging of AIDS-related polyradiculopathy. *Neurology* 1991, 41:1995–1997.
58. Murray RP, Kobayashi GS, Pfaller MA, Rosenthal KD: Picorna viruses. In *Medical Microbiology*, edn 2.. St. Louis: Mosby; 1994:583.
59. Rosencrance G: Images in clinical medicine. Herpes zoster. *N Engl J Med* 1994, 330:906.
60. Oxman MN, Levin MJ, Johnson GR, *et al*.: A vaccine to prevent herpes zoster and postherpetic neurologia in older adults. *N Engl J Med* 2005, 352:2271–2284.
61. Hope-Simpson R: The nature of herpes zoster: a long-term study and a new hypothesis. *Proc Roy Soc Med* 1965, 58:1–12.
62. Johnson RT, McArthur JC, Narayan O: The neurobiology of HIV infections. *FASEB J* 1988, 2:2970–2981.
63. Price RW, Brew BJ, Roke M: Central and peripheral nervous system complications of HIV-1 infections and AIDS. In *AIDS: Etiology, Diagnosis, Treatment, and Prevention*. Edited by DeVita VT, Hellman S, Rosenberg SA. Philadelphia: JB Lippincott; 1992:237–254.
64. Fauci AS, Lane HC: Human immunodeficiency virus disease: AIDS and related disorders. In *Harrison's Principles of Internal Medicine*, edn 16. Edited by Kasper DL, Braunwald E, Fauci AS, *et al*. New York: McGraw-Hill; 2005:1076–1139.
65. Olsen WL, Longo FM, Mills CM, Norman D: White matter disease in AIDS: findings at MR imaging. *Radiology* 1988, 169:445–448.
66. Hammer SM, Saag MS, Schechter M, *et al*.: Treatment for adult HIV infection: 2006 recommendations of the International AIDS Society—USA panel. *JAMA* 2006, 296:827–843.
67. Grindstaff P, Gruener G: The peripheral nervous system complications of HTLV-1 myelopathy (HAM/TSP) syndromes. *Semin Neurol* 2005, 25:315–327.

68. Rodgers-Johnson PEB, Ono SG, Asher DM, Gibbs CL: Tropical spastic paraparesis and HTLV-1 myelopathy: clinical features and pathogenesis. In *Immunologic Mechanisms in Neurologic and Psychiatric Disease*. Edited by Waksman BD. New York: Raven Press; 1990.

69. Izumo S, Goto MD, Itoyama MD, *et al*.: Interferon-alpha is effective in HTLV-1–associated myelopathy: a multicenter, randomized, double blind, controlled trial. *Neurology* 1996, 46:1016–1021.

70. Khalili K, White MK, Lublin F, *et al*.: Reactivation of JC virus and development of PML in patients with multiple sclerosis. *Neurology* 2007, 68:985–990.

71. Whiteman ML, Post MJ, Berger JK, *et al*.: Progressive multifocal leukoencephalopathy in 47 HIV-seropositive patients: neuroimaging with clinical and pathologic correlation. *Radiology* 1993, 187:233–240.

72. Bale JF Jr: Subacute sclerosing panencephalitis. A preventable disease that needs to be prevented. *Neurology* 2004, 63:1352–1353.

73. Ohya T, Martinez AJ, Jabbour JT, *et al*.: Subacute sclerosing panencephalitis. Correlation of clinical, neurophysiologic and neuropathologic findings. *Neurology* 1974, 24:211–218.

74. Weihl CC, Roos RP: Creutzfeldt-Jakob disease, new variant Creutzfeldt-Jakob disease, and bovine spongiform encephalopathy. *Neurol Clin* 1999, 17:835–859.

75. Brown P, Gibbs CJ Jr, Rodgers-Johnson P, *et al*.: Human spongiform encephalopathy: the NIH series of 300 cases of experimentally transmitted disease. *Ann Neurol* 1994, 35:513–529.

76. Jubelt B: Prion diseases. In *Merritt's Textbook of Neurology*, edn 11. Edited by Rowland LP. Philadelphia: Lippincott Williams & Wilkins; 2005:264–270.

77. Shiga Y, Miyazawa K, Sato S, *et al*.: Diffusion-weighted MRI abnormalities as an early diagnostic marker for Creutzfeldt-Jakob disease. *Neurology* 2004, 63: 443–449.

78. Will RG, Zeidler M, Stewart GE, *et al*.: Diagnosis of new variant Creutzfeldt-Jakob disease. *Ann Neurol* 2000, 47:575–582.

79. Manetto V, Medori R, Cortelli P, *et al*.: Fatal familial insomnia: clinical and pathologic study of five new cases. *Neurology* 1992, 42:312–319.

80. Perfect JR: Fungal meningitis. In *Infections of the Central Nervous System*, edn 3. Edited by Scheld WM, Whitley RJ, Marra CM. Philadelphia: Lippincott Williams & Wilkins; 2004:691–712.

81. Tunkel AR, Crous SE: Subacute and chronic meningitides. In *Atlas of Infectious Diseases: Central Nervous System and Eye Infections*, vol 3. Edited by Mandell GL, Bleck TP. Philadelphia: Current Medicine; 1995:2.13.

82. Gozdasoglu S, Ertem M, Buyukkececi Z, *et al*.: Fungal colonization and infection in children with acute leukemia and lymphoma during induction therapy. *Med Ped Oncol* 1999, 32:344–348.

83. Tucker T, Ellner JJ: Chronic meningitis. In *Infections of the Central Nervous System*. Edited by Scheld WM, Whitley RJ, Durack DT. New York: Raven Press; 1991:703–728.

84. Tunkel AR, Scheld WM: Central nervous system infections in the compromised host. In *Clinical Approach to Infection in the Compromised Host*, edn 3. Edited by Rubin RH, Young LS. New York: Plenum; 1994:187.

85. Galgiani JN: Coccidioidomycosis. *West J Med* 1993, 159:153–171.

86. Hildebrand J, Hildebrand M: Chronic meningitis. In *Infections of the Central Nervous System*, edn 3. Edited by Scheld WM, Whitley RJ, Marra CM. Philadelphia: Lippincott Williams & Wilkins; 2004:829–841.

87. Sepkowitz K, Armstrong D: Space-occupying fungal lesions. In *Infections of the Central Nervous System*, edn 2. Edited by Scheld WM, Whitley RJ, Durack DT. Philadelphia: Lippincott-Raven Publishing; 1997:741–762.

88. Simon RP: Neurosyphilis. *Arch Neurol* 1995, 42:606–613.

89. Stefanis L, Rowland LP: Spirochete infections: neurosyphilis. In *Merritt's Textbook of Neurology,* edn 11. Edited by Rowland LP. Philadelphia: Lippincott Williams & Wilkins; 2005:235–244.

90. Merrit HH, Adams RD, Solomon HC: *Neurosyphilis*. New York: Oxford University Press; 1946:24–67.

91. Simon R, Bayne L: Neurosyphilis. In *Infectious Diseases of the Central Nervous System*. Edited by Tyler KL, Martin JB. Philadelphia: FA Davis; 1993:237–255.

92. Davis E: Spirochetal disease. In *Diseases of the Nervous System: Clinical Neurobiology*, edn 2. Edited by Asbury AK, McKhann GM, McDonald WI. Philadelphia: WB Saunders; 1992:1359–1370.

93. Anderson JF: Epizootiology of Borrelia in Ixodes tick vectors and reservoir hosts. *Rev Infect Dis* 1989, 11(suppl 6):S1451–S1459.

94. Pachner AR, Steere AC: The triad of neurologic manifestations of Lyme disease, meningitis, cranial neuritis and radiculoneuritis. *Neurology* 1985, 35:47–53.

95. Coyle PK: Lyme disease. In *Current Diagnosis in Neurology*. Edited by Feldman E. St. Louis: CV Mosby; 1994:113.

96. Reik L Jr: Lyme disease. In *Infections of the Central Nervous System*, edn 2. Edited by Scheld WM, Whitley RJ, Durack DT. Philadelphia: Lippincott-Raven; 1997:685–718.

97. Cadavid D: Lyme disease and relapsing fever. In *Infections of the Central Nervous System*, edn 3. Edited by Scheld WM, Whitley RJ, Marra CM. Philadelphia: Lippincott Williams & Wilkins; 2004:659–690.

98. Coda GC: Protozoan and helminthic infections. In *Infections of the Central Nervous System*. Edited by Lambert HP. Philadelphia: BC Decker; 1991:264–282.

99. Johnson RT, Warren KS: Parasitic infections. In *Diseases of the Nervous System: Clinical Neurobiology*, edn 2. Edited by Asbury AK, McKhann GM, McDonald WI. Philadelphia: WB Saunders; 1992:1350–1358.

100. Luft BJ, Remington JS: Toxoplasmosis of the central nervous system. In *Current Topics in Infectious Diseases*, vol 6. Edited by Remington SJ, Swartz MN. New York: McGraw-Hill; 1985:315–358.

101. Berger JR: Parasitic diseases of the nervous system. In *Atlas of Infectious Diseases: Central Nervous System and Eye Infections*. Edited by Mandell GL, Bleck TP. Philadelphia: Current Medicine; 1995:5.4–5.25.

102. Farrar WE, Wood MJ, Innes JA, Tubbs H: *Infectious Diseases: Text and Color Atlas*, edn 2. London: Gower Medical Publishers; 1992:3.30.

103. Montoya JG, Kovacs JA, Remington JS: *Toxoplasma gondii*. In *Principles and Practice of Infectious Diseases*, edn 6. Edited by Mandell GL, Bennett JE, Dolin R. Philadelphia: Elsevier; 2005:3170–3198.

104. Oo MM, Aikawa M, Than T, *et al*.: Human cerebral malaria: a pathological study. *J Neuropathol Exp Neurol* 1987, 46:223–231.

105. Idro R, Jenkins NE, Newton CR: Pathogenesis, clinical features, and neurological out come of cerebral malaria. *Lancet Neurol* 2005, 4:827–840.

106. Kirchhoff LV: Trypanosomiasis. In *Infections of the Central Nervous System*, edn 3. Edited by Scheld WM, Whitley RJ, Marra CM. Philadelphia: Lippincott Williams & Wilkins; 2004:777–789.

107. Durack DT: Amebic infections. In *Infections of the Central Nervous System*, edn 2. Edited by Scheld WM, Whitley RJ, Durack DT. Philadelphia: Lippincott-Raven; 1997:831–844.

108. Maguire JH: Trematodes (Schistosomes) and other flukes. In *Principles and Practices of Infectious Diseases*, edn 6. Edited by Mandell GL, Bennett JE, Dolin R. Philadelphia: Elsevier; 2005:3276–3285.

109. Selwa LM, Brumberg JA, Mandell SH, Garofalo EA: Spinal cord schistosomiasis: a pediatric case mimicking intrinsic cord neoplasm. *Neurology* 1991, 41:755–757.

110. Cameron ML, Durack DT: Helminthic infections. In *Infections of the Central Nervous System*, edn 2. Edited by Scheld WM, Whitley RJ, Durack DT. New York: Raven Press; 1997:845–878.

111. Abbassioun K, Rahmat H, Ameli NO, Tafazoli M: Computerized tomography in hydatid cyst of the brain. *J Neurosurg* 1978, 49:408–411.